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THE USE OF STREPTOKINASE-STREPTODORNASE IN THE TREATMENT OF CHRONIC EMPYEMA*

WITH AN INTERPRETIVE DISCUSSION OF ENZYMATIC ACTIONS IN THE FIELD OF INTRATHORACIC DISEASES

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THIS article deals with the results obtained following the use of the streptococcal concentrates containing streptokinase-streptodornase (SK-SD)† in ten patients with chronic empyema, in nine of whom the disease ultimately developed from pulmonary tuberculosis.

Five of the patients were treated with the enzymes alone or in combination with antibiotic medication, and in five instances the use of SK-SD was associated with additional surgical procedures.

In addition to the detailed protocols of the cases described in this report, supplementary data derived from a relatively large number of other patients partially studied have been utilized to form the basis for a comprehensive discussion of the broad subject of the actions of SK-SD in a variety of intrathoracic diseases.

One of the special characteristics of the patients included in this report has been the long duration of the disease before enzymatic therapy was instituted. From the standpoint of the time in the course of their diseases at which the study of the effects of SK-SD was instituted, the patients were unselected. Consequently the stage in the empyema during which enzymatic treatment was introduced was fortuitous and, as will be subsequently discussed, this fact influenced the results from the standpoint of restoration of pulmonary function and alteration of pathologic changes in the tissues.

The single factor in common among the patients was the persistence of areas of local intrathoracic suppuration even though each of them had previ-

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ously received various forms of medical-surgical treatment that because of the inherent difficulties and refractoriness of the diseased state had not proved entirely successful.

However, in spite of the difficult conditions presented by the patients, it is believed that the favorable results to be described indicate the potentialities of this form of enzymatic therapy in chronic local infections of the thorax, and the findings also serve to define the requirements and conditions of further study.

Practical Management of Cases of Chronic Empyema.—

The use of SK-SD in this group has not followed as closely to a routine uniform regime as in the cases of closed empyema previously described,[1] since the conditions of disease varied widely. In view of the fact that the effectiveness of the enzymatic action depends on direct sustained contact between solution and area of exudative disease, both the technique of instillations and the number of repetitions of treatment have been adjusted to meet individual situations.

When open draining sinuses have been present the solution has been introduced with an appropriate catheter. (Foley catheters and thin plastic tubing have proved to be particularly useful.) After instillation, the exit has been closed by clamp or otherwise and the patient placed in an appropriate position to prevent leakage. Enzymatic action begins immediately but requires several hours to effect the maximum lysis to be expected from a single application. According to the size of the infected area, therefore, the duration of contact with SK-SD is maintained from four to eight hours in small residual pockets, and from twelve to sixteen hours in larger ones.

Open, free drainage with removal of the catheter is then particularly important and desirable.

Dosage: A solution containing approximately 10,000 units SK and 4,000 units SD per cubic centimeter has been introduced into the cavities according to their capacity up to 20 cubic centimeters. Variations in the amount of solution introduced have occurred according to special circumstances of individual cases.

Most of the patients of this group have received repeated treatments extending over varying periods of time. Our policy in general has been to treat daily for four to five days, leaving the solution in situ as indicated above, followed by open drainage, until the following day. Upon completion of a series of four to five treatments, the procedure is suspended for three to four days in order to evaluate the effect. Repetitions of the injections in series have been employed so long as evidence of favorable response is demonstrable. When optimum effects are obtained they consist in: (a) an immediate increase in the amount of exudate following first few instillations; (b) beginning change in the character of exudate from coarse to a thinning fluid often becoming slightly sanguineous; (c) beginning appearance of fresh granulation tissue when the wounds are visible; (d) decrease and disappearance of bacterial flora; (e) cessation of drainage and closure of sinus tract. Daily quantitative bacteriologic colony counts have proved particularly useful (see Charts) since progressive decreases in the number of bacteria provide specific information not reflected in routine nonquantitative broth cultures.

TABLE I. TREATED WITH SK-SD ALONE

PATIENT	PRESENTING DISEASE	BACT. CULTURES (PRE SK-SD)		NO. INSTILLATIONS OF SK-SD	ANTIBIOTIC* (CONCOMITANT)	RESULT	
		M. TUBERCULOSIS	OTHER ORGANISMS			EARLY	FOLLOW-UP†
1. K. T.	Residual postoperative empyema with draining sinus tract	+	*Staph. aureus*	9	1. Aureomycin (L) 2. Chloramphenicol (S)	Healed	1 year
2. M. H.	Residual postoperative empyema with draining sinus tract	+	*Staph. aureus* *B. alkaligines*	7	Aureomycin (S) with chloramphenicol (L)	Healed	9 months
3. P. W.	Residual postoperative empyema with draining sinus tract	–	*Staph. aureus* *B. pyocyaneus*	9		Healed	Relapse at 6 months
4. A. B.	1. Residual postoperative empyema with tubal drainage 2. Subpectoral abscess	No culture	Mixed unidentified flora	3	Penicillin (S)	Healed	6 months
5. E. B.	1. Residual postoperative empyema with draining sinus tract 2. Subscapular abscess	+ +	— —	10 10	— —	No effect No effect	Died at 6 months—brain abscess

*(L) indicates Local, (S) indicates Systemic Route of Administration.
†Time stated indicates last observation.

It will be noted that one or more antibiotic reagents were employed coincident with SK-SD instillations. Their selection was based frequently on the results of in vitro sensitivity tests, but on other occasions the organisms were characterized by total resistance. The advantageousness of combined enzymatic-antibiotic therapy will be subsequently discussed.

When sterility has been obtained we have come to believe it important to remove any drainage tubes that may be present and to permit healing to occur spontaneously.

The transient pyrogenic reactions which may follow the injection has been previously referred to,[2] and the total toxic reactions, none of which have proved to be serious, have been described in detail.[3] The administration of amidopyrine (0.6 Gm. four times a day) on the day preceding and the day of treatment has abolished the thermal reaction and abated considerably the symptomatology. Aspirin has proved useful but less effective than amidopyrine.

Clinical Data.—

I. *Five patients were treated with SK-SD alone* or in association with antibiotic medication.

Pertinent data of each are tabulated in Table I.

Brief protocols of each of the five cases are presented together with charts referable to 3 of them.

CASE REPORTS

CASE 1.—Patient K. T., 27-year-old Negro man. Postoperative residual empyema with spontaneous draining sinus.

Pulmonary tuberculosis was first discovered in 1944. He subsequently developed tuberculous empyema. A Schede thoracoplasty was performed over the lower right chest in 1946, and in July, 1947, a revision operation was performed to obliterate the remaining empyema space. Early in 1948 the patient was readmitted to the hospital because of a persistent draining sinus in the right posterior thoracic wall. Late in 1948 the sinus was excised and a muscleplasty was performed along with decortication of the lung and deroofing of the space. In July, 1949, an abscess formed under the operative scar and began to drain. Drainage had been continuous for five months prior to admission to our Service. Cultures of exudate were positive for *M. tuberculosis* and also for hemolytic *Staphylococcus aureus.*

From the roentgenogram of Fig. 1, the extent of the initial enlargement of the residual space following three instillations of solutions of SK-SD (180,000 and 60,000 units) is evident from the increase in the size of the area containing diodrast. The period of enlarging which is accounted for by the elimination of the local accumulations of deposits of exudate, was attended by an increase in the amount of drainage. Following five instillations of SK-SD, treatment was suspended. As the infection subsided the drainage became serous in character and decreased in amount but persisted. Fresh granulation tissue became visible externally to indicate healing. The size of the infected area was reduced in size so that no diodrast was accommodated. Following reinstitution of SK-SD therapy drainage ceased completely and closure of sinus followed promptly.

In the Chart in the lower part of Fig. 1, the details of the bacteriological findings and the periods of antibiotic therapy are given: From the data it may be noted that the staphylococcus aureus disappeared promptly following the administration of SK-SD and aureomycin. Cultures for M. tuberculosis, however, remained positive.

When the colony count of staphylococcus aureus rose again enzymatic therapy was reinstituted together with chloramphenicol. Within four days of the last treatment, the cocci disappeared permanently.

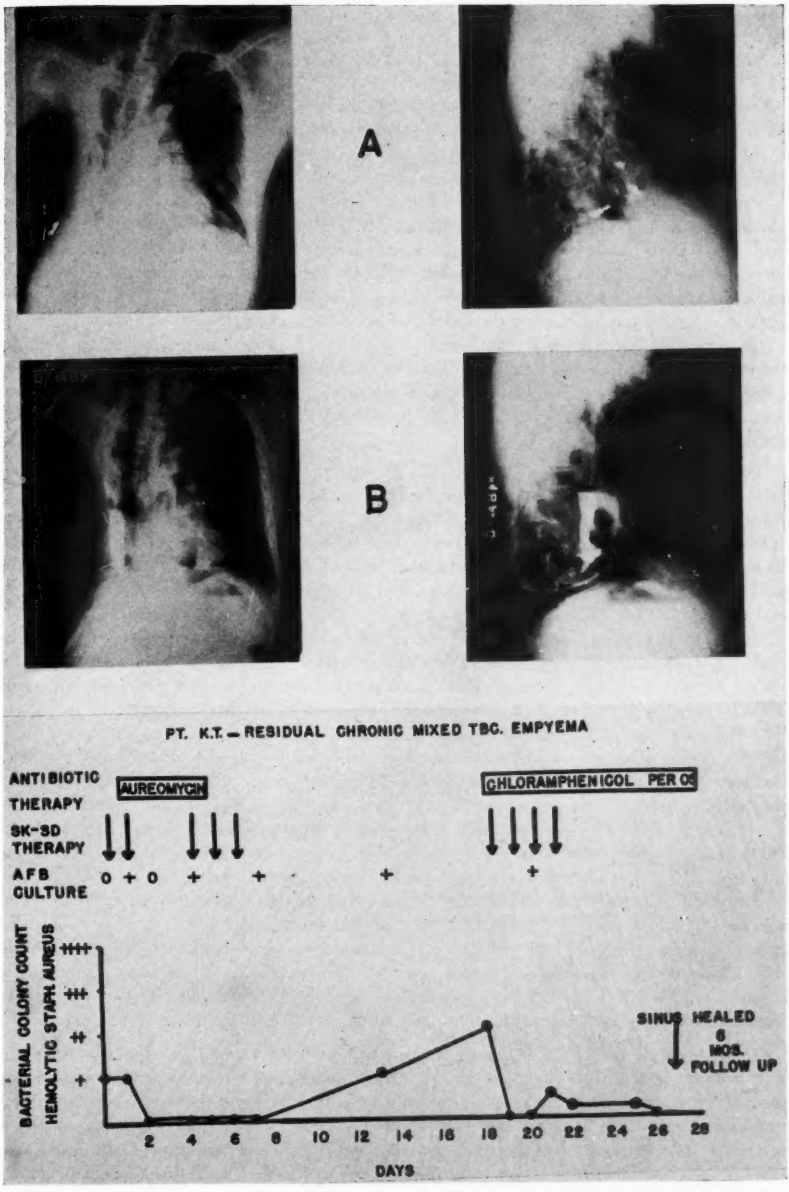

Fig. 1.—Case K. T. Chronic residual mixed tuberculous empyema with draining sinus. (Diodrast Studies.) *A.*, Posteroanterior and lateral appearances prior to SK-SD therapy. Note the inefectual outlining of the residual empyema space by diodrast. *B.*, Posteroanterior and lateral appearance after one week's course of SK-SD therapy. Diodrast filled space outlined and considerably enlarged. *C.*, Graphic summary of clinical and bacteriologic course. (See text.)

CASE 2.—Patient M. H., 30 years old, white woman. Postoperative residual empyema with draining sinus. Pulmonary tuberculosis was known to have been present since 1939. Left pneumothorax was maintained from 1943 to 1948. Tuberculous empyema developed in 1948. A closed thoracotomy was performed in February, 1949. A bronchopleural fistula developed. Left pneumonectomy was performed later in 1949 followed by two stages of thoracoplasty. Drainage tube was left in situ during and following the operations. On removal of the tube, a residual pleural pocket remained with an open sinus tract in the left axilla. SK-SD therapy was begun four months later.

From the diodrast studies shown in Fig. 2, the changes in the residual pocket indicate the reduction in the size of the area as influenced by the instillations of SK-SD. When, during the period of improvement, the sinus tract was probed, the thin material that exuded was stained with fresh blood. On the basis of other direct observations on open wounds this finding was interpreted as a sign of the presence of fresh granulation tissue, the exuberant growth of which has markedly decreased the size of the residual space.

The bacteriologic chart in the lower part of Fig. 2 shows the effect of the combined enzymatic action and antibiotic administration on *Staphylococcus aureus* and *B. alkaligines.* The drainage changed to a serous character two days after the abolition of positive cultures of the mixed secondary infection, and the sinus tract healed over the next six weeks without medication.

CASE 3.—Patient P. W. Early in 1949 this patient developed pyopneumothorax from which *Staphylococcus aureus* was cultured. The infection was refractory to therapy by drainage through thoracotomy and penicillin. Because of suspected underlying tuberculosis, pneumonectomy was performed followed within a month by thoracoplasty. A purulent drainage persisted with *Staphylococcus aureus* and *B. pyocyaneus* being present. No tuberculosis was demonstrated. He was transferred to our service two months after the thoracoplasty, having drained continuously for ten months.

In roentgenogram *A* (Fig. 3), the residual space is filled with diodrast which outlines its size and position; the thoracic asymmetry resulted from the thoracoplastic operation. Roentgenogram *B* (Fig. 3), reflects the appearance of the chest after drainage had ceased and the sinus closed. There was no longer an area into which diodrast could be introduced.

Below the roentgenogram in Fig. 3 is a bacteriologic chart.

The two organisms present were *Staphylococcus aureus,* found by tests to be sensitive to aureomycin, and *B. pyocyaneus,* resistant to aureomycin. The arrows at the bottom indicate individual SK-SD treatment.

The first period of sterilization was rapidly accomplished. But when enzymatic therapy was stopped, the staphylococcus having been abolished completely by the combination of SK-SD plus aureomycin, the pyocyaneus bacillus returned.

Enzymatic instillations were again instituted without aureomycin. Sterility was again accomplished. At this point in the treatment, a drainage tube which had been kept in place continuously was removed since it appeared to serve as a contaminating foreign body. The patient was seen at regular intervals, and the sinus tract remained closed for six months. However, although not available for further treatment, the patient was known to have developed either reinfection or new infection in the same area.

CASE 4.—Patient A. B., 48 years old, white man with known tuberculosis since 1925. Right pneumothorax was continued until 1944. Lung failed to reexpand due to calcific deposits in pleura. In January, 1950, he developed an upper respiratory infection followed by right thoracic pain. On admission to the hospital in March, 1950, a purulent empyema was found to be present, and because bronchopleural fistula was suspected a closed thoracotomy was performed. By culture the fluid contained mixed unidentified organisms.

Three states of thoracoplasty with drainage continuing were performed at approximately ten-day intervals. The exudate was sanguinopurulent and contained, by culture, enterococci and diphtheroids.

After ten days of continuous drainage, following the last thoracoplasty, three daily instillations of SK-SD (180,000 units and 63,000 units) were given. The exudate became serous, and on the third day post-SK-SD, the sinus closed.

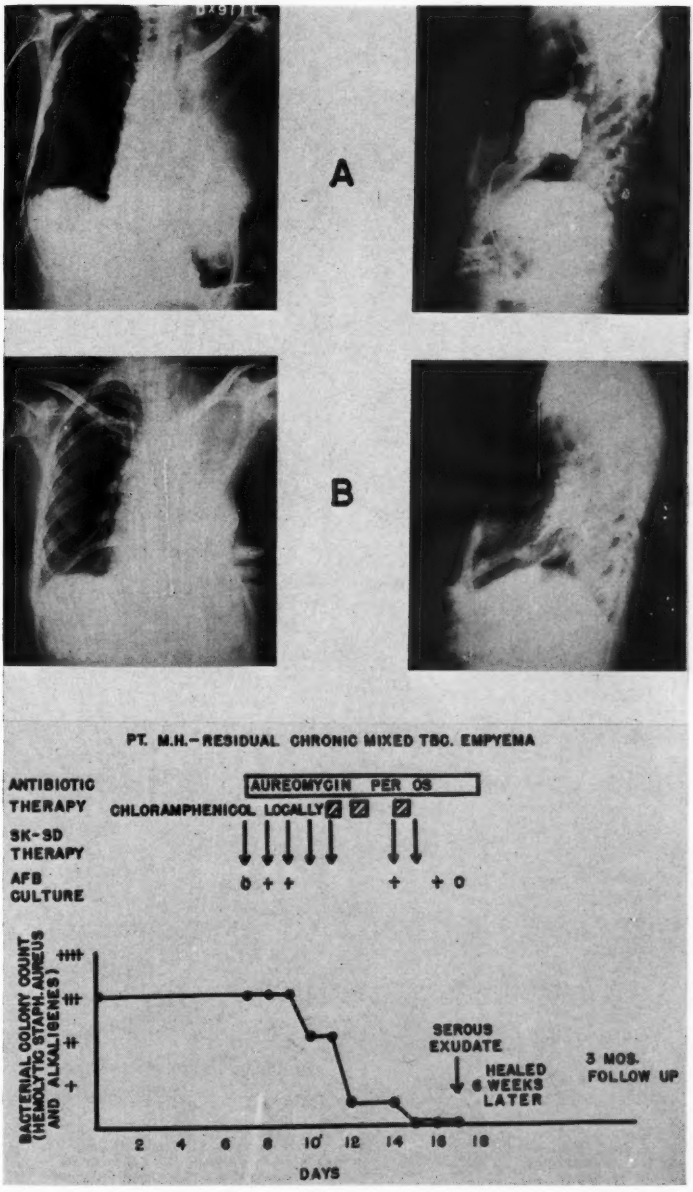

Fig. 2.—Case M. H. Chronic residual mixed tuberculous empyema with draining sinus. (Diodrast studies.) *A.*, Posteroanterior and lateral appearances after first instillations of SK-SD indicating size and shape of cavity. *B.*, Posteronanterior and lateral appearances three weeks after completion of course of SK-SD therapy, indicating decrease in size of area with irregular edges suggesting ingrowth of granulation tissue. *C.*, Graphic summary of clinical and bacteriological course. (See text.)

TABLE II. TREATED WITH SK-SD PLUS SURGERY

PATIENT	PRESENTING DISEASE	BACT. CULTURES (PRE SK-SD)		NO. INSTILLATIONS OF SK-SD	SUBSEQUENT OPERATION	POSTOPERATIVE RESULT	
		M. TUBERCULOSIS	OTHER ORGANISMS			EARLY	FOLLOW-UP†
1. N. M.	Empyema with draining sinus	+	—	1	Right upper thoracoplasty and lobectomy, decortication of middle and right lower lobes	Healed	3 months
2. H. K.	Residual postoperative empyema with tubal drainage	No culture*	*B. coli* *Staph. aureus* yeast	6	Thoracoplasty, pleuropneumonectomy	Healed	6 months
3. W. W.	Residual postoperative empyema, intermittent spontaneous drainage	+	—	1	Plastic Repair	Healed	2 years
4. E. W.	Closed empyema	No culture*	—	3	Decortication, right upper lobectomy	Partial effect SK-SD	
5. L. M.	Closed empyema	No culture*	—	4	Decortication	No effect SK-SD	

*Known case of tuberculosis.
†Time stated indicates last observation.

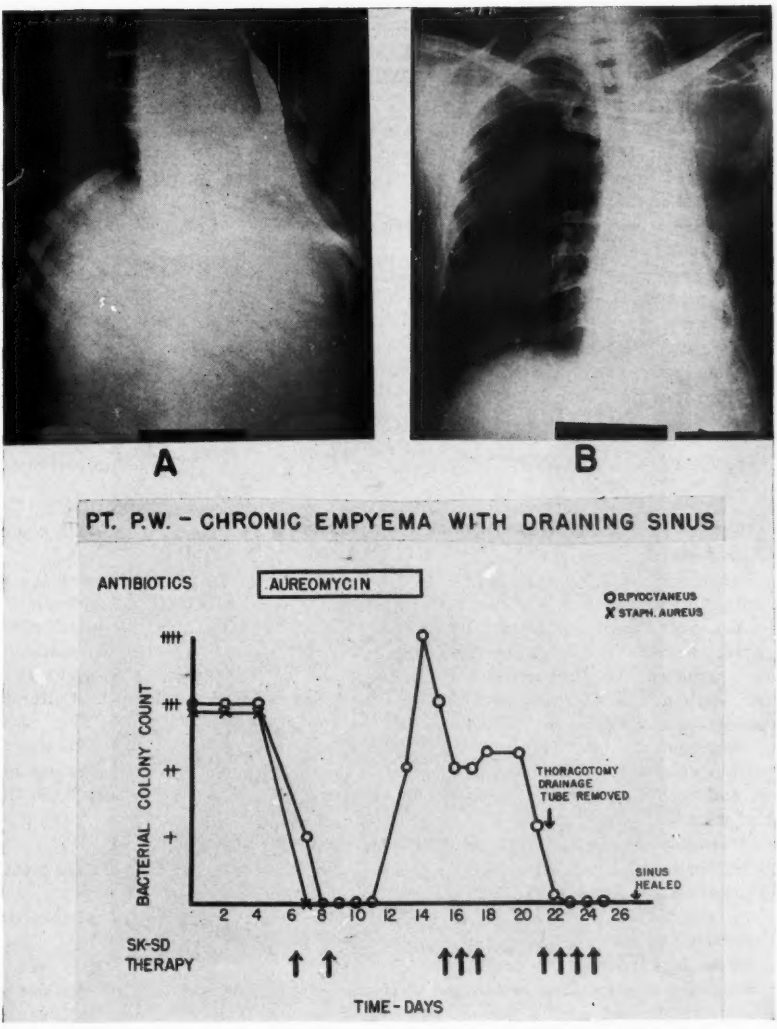

Fig. 3.—Case P. W. Chronic residual nontuberculous empyema with draining sinus. (Diodrast studies.) *A.*, Indicates posteroanterior appearance of cavity after 1st 2 instillations of SK-SD. *B.*, Indicates posteroanterior appearance after closure of sinus. *C.*, Graphic summary of clinical and bacteriologic course. (See text.)

Subsequently, an infection developed in the subpectoral space formed during mobilization of the muscles for the anterior thoracoplasty. Enterococci and staphylococci were isolated from this area.

Into this additional space the patient received daily instillations of SK-SD (180,000 and 63,000 units) for eight days. The infection cleared and the space closed five days after the last treatment.

No additional antibiotics were employed other than penicillin, which the patient had been receiving since admission.

CASE 5.—Patient E. B., 42-year-old white man. Pleuropneumonectomy for tuberculosis with the subsequent development of empyema necessitans. Two months after the operation mentioned above empyema developed which was drained by rib resection followed by two stages of thoracoplasty.

The patient was transferred to our service after a period of six months, during which no change in his condition had occurred.

Roentgenogram examinations with lipiodal revealed two spaces—one in the subscapular area of the extrathoracic wall, and the other extending within the thorax. *M. tuberculosis* was abundantly present in direct smears of exudate, indicating a massive infection.

The patient received intensive therapy with multiple instillations of SK-SD into both residual spaces over a two-week period without any significant change. *M. tuberculosis* continued to be just as numerous by direct microscopic examination of exudate after SK-SD as before.

II. *Five patients were treated with SK-SD* and subsequent operative procedures. Data are given in Table II.

CASE 6.—Patient N. M., 52 years old, white man. Tuberculous empyema with a needle tract sinus draining to exterior.

Tuberculosis of the right lung was discovered in 1944. During the next one and one half years the patient was treated with pneumothorax and pneumolysis. Repetitions of pneumothorax were continued until August, 1948. In January, 1947, a pleural effusion appeared, the character of which gradually changed until it became thick, viscid, and grossly purulent. In May, 1948, a draining sinus tract appeared in the right lateral thoracic wall at the site through which pneumonolysis had been performed. Cultures of the exudate were positive for *M. tuberculosis.*

Treatment was undertaken by our service two months later. The following observations were made. The first specimen of fluid obtained by thoracentesis was unusually thick, and no sediment would separate on centrifugation. It had a viscosity 3,000 times that of water.

A solution containing 100,000 units SK plus 7,200 units SD was injected.

Within four hours a sample of the pleural exudate had only 37 per cent sediment on centrifugation and viscosity of thirty-three times that of water.

On the following day, 50 c.c. of greenish yellow fluid was obtained, thirteen times the viscosity of water. The sinus tract was no longer draining.

Three days later the sinus tract closed.

Over the ensuing three weeks the character of the fluid obtained by thoracentesis progressively changed until it became serosanguineous with only 2 per cent sediment, and no sinus tracts opened at the site of the needle punctures.

Although the amount of fluid decreased substantially, the lung could not be reexpanded even with high negative intrapleural pressure because of the thickened peel incarcerating the lung. Upper thoracoplasty was performed approximately one month after the instillation of SK-SD, followed a month later by right upper lobe lobectomy and decortication of the right middle and lower lobes.

No evidence of empyema reappeared. The patient was discharged for sanatorium care without evidence of residual empyema.

CASE 7.—Patient H. K., 38 years old, Negro man with known pulmonary tuberculosis since 1936. Right pneumothorax was instituted prior to right upper lobectomy. A pleural effusion appeared in 1940 and continued to be present for four years. An abscess of the external thoracic wall developed in 1949 and was incised and drained. Later that same year the pleural effusion reappeared, and after six months both the pleural exudate and sputum suddenly became foul. A course of streptomycin was administered without noticeable effect. A bronchopleural fistula was not demonstrated.

An open thoracotomy was performed. Considerable quantities of foul purulent fluid were removed. Cultures were positive for *B. coli*, staphylococci, and a yeast.

One week later the patient was started on a course of SK-SD treatments with appropriate antibiotics. He received instillations twice daily for three days. Cultures were sterile by the fourth day.

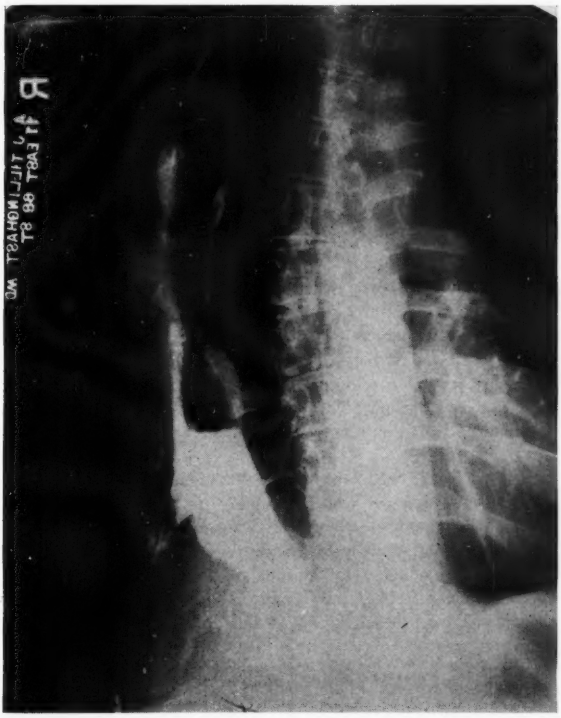

Fig. 4.—Case W. W. Chronic residual tuberculous empyema. Roentgenogram indicates appearance of cavity just prior to surgical operation. (See text.)

Four days post SK-SD a right pleuropneumonectomy was performed. A small bronchopleural fistula was observed at the area of the lower lobe. The thorax was closed without drainage. At operation both pleural surfaces were observed to have a clean reddened granular appearance. During a six-month period of postoperative observation the patient has remained well.

*This patient was observed and treated by Dr. Laurence Miscall (Assistant Professor of Clinical Surgery, Cornell University Medical College, New York). The abstract and photograph of Fig. 4 are presented with his approval.

CASE 8.—Patient W. W.,* 49 years old, white male. Pulmonary tuberculosis was detected in 1940 with the subsequent development of bilateral upper lobe cavitation. Later in 1940 a right pneumothorax was given followed by right pneumolysis. Empyema developed; the pleural effusion contained *M. tuberculosis.* During the same year two stages of thoracoplasty were performed. In spite of repeated aspirations an unhealed tuberculous empyema persisted which has drained intermittently to the exterior until enzymatic-surgical procedures were employed.

Other measures employed between 1941 to 1948 were partial Schede operation and repeated courses of streptomycin. Intermittent incidents of spontaneous drainage continued, and have recently become more frequent.

At the time of hospitalization, with which this report is concerned, a large empyemal space was present with multiple draining sinuses. (See diodrast visualization of Fig. 4). The exudative material was very thick and creamy, and was aspirated through a medium sized catheter; it contained *M. tuberculosis.*

A solution containing 200,000 units SK and 60,000 units SD was instilled. Twenty-four hours later the fluid had become considerably thinner and slightly sanguineous. After forty-eight hours the fluid was watery in consistency and blood tinged.

Four days later, the empyemal space was opened in the operating room. Instead of encountering dirty gray pleural surfaces both the parietal and visceral pleurae appeared clean with early granulation tissue. The parietal pleura, which proved to be resilient instead of inelastic, was mobilized in the superior portion from the regenerated ribs. The thoracic wall was closed with a small catheter placed in the lower pocket in the costophrenic sinus. The catheter was removed on the third postoperative day, and silk sutures were removed on the fifth postoperative day. The wall healed by primary union, and has remained so during two years of follow-up.

CASE 9.—Patient E. W., 24-year-old white man, with known pulmonary tuberculosis for one and one half years. Right pneumothorax instituted with discovery of disease.

On admission to hospital empyema was present. Aspirated fluid was thick and purulent. Loculated areas were evident by roentgenogram.

In preparation for resection of one lobe and decortication, three injections of SK-SD were given over a five-day period. The character of the post-treatment samples of fluid became serosanguineous, and the amount decreased substantially. The loculations disappeared.

At operation a single sac was present which extended from the diaphragm to a point near the apex. The inner surface was irregularly nodular and granular. There was no debris or caseouslike particles present. There was no pus to soil the area. Decortication and right upper lobe lobectomy were performed.

Although the fixed residual solid tissues of the pleura, as seen at operation, was not significantly altered by SK-SD, the enzymatically cleansed surface was such as to promote better coaptation and sealing by fusion for contemplated thoracoplasty in this type of patient.

CASE 10.—Patient L. M., 44-year-old Puerto Rican man. Known tuberculosis for two and one-half years, and left pneumothorax for two years. When seropurulent fluid developed under observation, decortication and lobectomy was planned.

Before operation four injections of SK-SD were given over a ten-day period, each injection followed by thorough aspiration within twenty-four hours. No objective changes were noted by roentgenogram.

When decortication was performed ten days later, the lung was found to be covered by a thick "collagenous peel" which was unaffected by the enzymes.

DISCUSSION

This article is the third in a series that has dealt primarily with the results derived from the use of streptokinase-streptodornase in groups of diseases of

the thoracic area. One of the previous reports concerned hemothorax,[4] and another one postpneumonic empyema.[1] In each, factors special to the disease entities under treatment were taken into account in addition to the general principles of enzymatic clinical therapeusis which have proved to be applicable irrespective of the anatomic locations of extravascular hemorrhagic deposits or exudative diseases of infectional origin.[2, 5]

In the patients with chronic empyema special conditions referable to the protracted nature of the diseased states of the pleurae and lungs were present, which, according to the response to therapy, have served to define more broadly the mode of action of SK-SD by which clinical effects have been obtained. In addition to matters of practical therapy, factors pertinent to the essential nature of chronic infections have emerged that were based on the differing types of responses exhibited at the sites of disease. In the latter respect, therefore, through the observed effects, the application of the streptococcal enzymatic material has served as a specialized technique for gaining particular information concerning the infections and their pathology.

For purposes of broad discussion the findings may be divided into two categories consisting of the *infection itself* and the *state of the tissues.* Information derived from individual unpublished observations in cases of various types of empyema have supplemented the detailed case reports in contributing to the ensuing analysis.

The Infection: From the standpoint of the mixed microbial flora involved in chronic infections, the different bacterial species that may be considered secondary invaders were in most instances successfully eradicated and not infrequently with considerable rapidity. The essential principles by which the local enzymatic actions operate to promote local bacterial sterilization have been previously discussed,[3] and need not be recapitulated here. In extension of a consideration of the subject, however, additional points of interest with respect to the conditions existing at the site of the infection that influence the outcome of enzymatic therapy have been indicated by the response of patients with chronic empyema as well as other cases of chronic infections located in different sites of the body.[3, 5, 6]

One factor appears to be related to the depth within the tissues to which viable bacteria extend as revealed by the extent to which the topical enzymatic actions promoted suppression of the microorganisms. Since the direct action of the enzymes is, in a sense, a surface phenomenon, when both bacterial sterilization and healing have occurred rapidly the results have indicated that the areas of active infection at the time of the instillations of SK-SD were relatively superficial. In patients with infections of several months or years duration who have been successfully treated it has been surprising to observe the rapid disappearance of the chronic activity even though it had previously failed to respond to other forms of standard treatment and even though the pathologic anatomic alterations of the tissues were extensive. Furthermore, the effectiveness of the instillations of SK-SD in inducing sterilization has not been regularly predictable based on duration of infection. On the basis of the findings just outlined it seems reasonable to conclude that the deep subsurface areas of

pathology have constituted "burned out" areas of earlier stages of either the primary or secondary infection (with no viable organisms now present) which have however not deterred post-SK-SD healing.

In patients whose infections have been entirely refractory to enzymatic therapy, on the same basis it seems evident that either the depth to which viable bacteria extended—or other undetermined factors—were such that solutions of SK-SD did not make proper contact with the total areas of disease, and, as a consequence, the infection was not influenced by the enzymatic effects. The negative results have therefore contributed to an understanding of certain aspects of the infection not previously apparent, and they have served to indicate that other therapeutic measures involving the planned use of surgical-antibiotic-enzymatic procedures are required appropriate to the newly defined problem.

In patients with chronic protracted infections in whom the use of SK-SD was followed by a partially favorable effect (reduction in number of organisms and partial local clearing but not sterilization) the contributions which enzymatic applications have made to defining the nature of infection has been elaborated in other articles and need not be discussed here except to point out that fixed foreign substances (nondetachable pieces of dead tissue, sutures, etc.) have been the basis for refractoriness; their removal subsequent to the identification has successfully eradicated the disease.

The effect of enzymatic therapy in promoting the efficacy of antibiotic medication has been extensively observed and has contributed to the outcome of some of the cases of chronic empyema. The liquefying action has been found to promote both the increased distribution of antibiotics introduced locally by eliminating the obstruction imposed by thick exudates and also the diffusion from the general circulation to the local area. However, in some instances organisms possessing multiple antibiotic resistance also were eradicated, the response being referable to the antibacterial qualities of the tissues themselves.

The different types of circumstances elaborated in the discussion just given for chronic infections in general are suggestively significant in interpreting the results of cultures for *M. tuberculosis,* although these results are not yet so sharply defined. In the cultures for tubercle bacilli quantitative methods were not employed. Consequently, reductions in the number of colonies, which were a useful means of estimating the effect of the enzymes on the other bacteria, was not noted. Furthermore, an intermittency in the positive or negative results of single cultures of *M. tuberculosis* cultures may have been a chance circumstance. Consequently, an analysis of the reports on the growth or sterility of *M. tuberculosis* by culture has certain limitations, which are further conditioned by the special characteristics of chronic tuberculous changes as contrasted with those occurring in chronic pyogenic bacterial diseases.

However, there is considerable evidence that the antibacterial factors of enzymatic therapy that have proved to be effective against various bacterial species are also successfully operative against *M. tuberculosis,* since local sup-

purative tuberculous lesions have been eradicated in association with SK-SD therapy, in a manner comparable to that occurring in other forms of local chronic disease.[7]

Including unpublished observations on cases partially or incompletely studied for total effect of SK-SD, the following types of changes have been noted in serial cultures for *M. tuberculosis* during SK-SD instillations:

1. Cultures repeatedly positive have changed to cultures repeatedly negative. These results are entirely similar to others that have occurred in infections due to pyogenic and saprophytic organisms that have cleared completely and promptly.

2. Cultures from sites containing thick loculated purulent exudates have changed from pre-SK-SD negative results to positive findings during therapy and then to a final negative. The uncovering of viable organisms, contained in thick exudative coverings and loculations by enzymatic liquefaction and their subsequent eradication with and without antibiotic medication has been repeatedly observed in infections due to pyogenic and saprophytic organisms.[4, 5]

Up to the present time the release of imbedded *M. tuberculosis* has not been followed by a demonstrable spread of infection, although the potentialities of this complication have been recognized.

3. Culture for *M. Tuberculosis* have continued positive before, during, and after enzymatic applications. Under such conditions no effect of SK-SD on the infection has been observed. Patient E. B. of Group I illustrates such a negative result.

In spite of the characteristics peculiar to chronic tuberculous changes, it may be tentatively concluded that in some patients, the basis for the favorable response in local tuberculosis is not dissimilar to that responsible for the curative results obtained in all successfully treated cases. Continued experimental and clinical studies on the action of SK-SD in tuberculosis are in progress in order to evaluate more clearly this phase of the total subject.

The *state of the tissues* at the site of the active inflammatory diseases before, during, and after instillations of SK-SD has also been a subject of considerable interest. The importance of this problem in cases of empyema is apparent since the type and extent of the pathologic changes that have occurred in and on the pleurae determine the extent to which pulmonary function or thoracic anatomic disfiguration may be favorably affected through solutions of SK-SD, even though the infection is abolished.

In our studies of cases of hemothorax[3] and postpneumonic empyema[1] the time in the course of the diseases at which the restoration of pulmonary expansion may be most rapidly and completely attained by enzymatic lysis of pleural contents and aspiration has been given special consideration. In the patients of the previous groups who exhibited the least favorable response to the treatment it appeared probable that either cellular organization or the presence of special types of pathologic deposits had occurred to a degree that represented irreversible tissue changes. Since neither fully organized cellular tissues (fibrosis) nor such acellular pathologic substances as collagen are altered by SK-SD, changes in the anatomic state of the pleurae have not been

effected in cases of protracted empyema where the above conditions had become established before treatment was instituted. However, in spite of the anatomic difficulties, the abolition of the residual infection has resulted either in spontaneous healing with regrowth of fresh granulation tissue or in affording a clean operative field for subsequent surgical renovation.

The planned use of SK-SD in preparation for subsequent operative procedures designed to free the lung or close residual spaces by excising pathologic tissues that are not amenable to lysis is illustrated in the patients with chronic empyema of Group II.

In the first three cases of Table II it seems clear that the enzymatic cleansing of the tissues afforded: (a) clean and sterile field in which to operate, and (b) surfaces exhibiting fresh granulation tissue to effect healing, per primum. Cases 4 and 5 have been included to illustrate a partially favorable result and a negative result in which the limitations of the effectiveness of SK-SD was accounted for by the nature of the fixed pathologic tissues observed at operation.

Bronchopleural Fistulae: In patients with chronic empyema of original tuberculous etiology, problems associated with the reopening of fistulae have been well recognized. Although not described in detail in this article, in several instances—with patients treated at this hospital and at other institutions—previously existing bronchopleural fistulae have been reopened following the liquefying action of the enzymes and has constituted an undesirable complication, either by making local management more difficult or by possibly creating an intrabronchial route for the transmission of tubercle bacilli to the opposite lung fields. However, in individual cases, the fistulae after opening have been observed to close again. Pleurocutaneous fistulae have frequently been observed to close following instillations of SK-SD.

In our studies of this problem, which are as yet incomplete, factors referable on the one hand to local conditions influencing the completeness of the cleansing enzymatic effect and on the other hand to the resiliency of the tissues surrounding the fistulae, appear to be particularly significant in determining whether or not the use of the enzymes are automatically contraindicated when intrapulmonary tuberculous fistulae are present or whether their planned use may in selected cases be particularly useful in difficult refractory situations.

In connection with the subject of the deposition of pathologic substances at the site of chronic infections, our experience has suggested that neither the rate nor extent of their development are regularly constant but appear to be dependent on factors, as yet undetermined, in the response of the tissues to infectional insults. In this field our studies are being directed toward attempting to determine the biochemical entities that comprise the diseased tissues in order that advantage may be taken of the specificities of enzymatic action in relation to the essential composition of the substrates to be acted upon. From the standpoint of experimental enzymology, preliminary studies

indicate the complexity of the subject. However, when account is taken of the great diversity of enzymes of all types available in nature, the subject invites more extensive investigations.

It is finally concluded by us that if the special advantages to be obtained by the use of SK-SD are to be utilized for greatest effectiveness in patients with empyema or hemothorax, the enzymatic form of therapy should be employed *before* the difficulties inherent in chronicity have become established.

The total additional studies that are required to define more clearly the problems indicated in the preceding discussion are apparent and it is hoped that the comments may invoke active investigational interest in the field of intrathoracic diseases.

SUMMARY

The detailed courses of ten patients with chronic protracted empyema who were treated with instillations of solutions of streptococcal concentrates containing streptokinase-streptodornase (SK-SD) have been described as illustrative of the successful, partially successful, and unsuccessful results of local enzymatic therapy.

Among five of them treated with SK-SD plus antibiotic reagents, four healed relatively rapidly, one of which suffered relapse or had reinfection six months later.

In the remaining five patients, the use of SK-SD was purposefully instituted in preparation for subsequent surgical procedures. In three of them, the enzymes afforded a sterile field in which to operate, and the presence of fresh granulation tissue was observed; in one a partial effect was obtained; in one no effect of the enzymes was observed on the pathologic tissues.

An extended discussion of the actions of SK-SD has been given in order to indicate both the potentialities of enzymatic therapy as a practical measure and also as a special method of investigation into the underlying characteristics of chronic infections.

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SERUM PROTEIN LEVELS AND CALCULATED OSMOTIC PRESSURES IN TUBERCULOSIS: I. CORRELATION OF THESE VALUES WITH THE SEVERITY OF THE DISEASE*

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THE present investigation of serum proteins in pulmonary tuberculosis was instigated more or less directly by experimental observations on dogs[1] in which acute hemorrhage was found to cause pulmonary edema. A coincidental finding of these experiments on hemorrhage showed that acute reduction of the total serum protein by as little as 0.8 Gm. to 1.0 Gm. per 100 ml. of serum as a result of the intravenous administration of physiologic sodium chloride would also produce edema of the lung. The pulmonary edema was demonstrated in both of these animal experiments by dehydration procedures and by histologic section of the lungs, and it was a consistent observation even when the moisture increase was too little to be clinically apparent.

It is recognized that the serum proteins are of great value in maintaining the normal osmotic pressure of blood, and that the osmotic pressure, in turn, is of importance in regulating the equilibrium of tissue fluids. Because of the possibility that edema of the lung may contribute to the pathogenesis of pulmonary disease, it seemed possible that a lowered serum protein level might be a detrimental factor in any infectious disease of the lung by virtue of the pulmonary edema it could induce. The concept received encouragement by the favorable clinical results observed with plasma therapy in several children with pneumonia resistant to other treatment.[2] In these patients it was found that the total serum protein, the serum albumin, the albumin-globulin ratio, and the calculated osmotic pressure were all low; and intravenous plasma was given these patients for the purpose of restoring the low serum protein values to the normal, hence raising the osmotic pressure and reducing lung edema.

It seemed possible that in pulmonary tuberculosis the presence of edema of the lung could also be a contributing factor to the pathogenesis of this disease, and that edema might be present more frequently than is realized in association with lowered serum proteins. Seibert and Nelson[3] demonstrated by electrophoretic patterns with sera from animals with experimental tuberculosis that there was a consistent decrease in the serum albumin level and a rise in beta-globulin, which could be detected as early as ten days to two weeks following the infective inoculation. In several cases of human tuberculosis these authors noted abnormally low serum protein values which seemed to parallel the clinical

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course of the disease. It could well be, therefore, that depletion of the serum proteins with the resultant lowering of the osmotic pressure of the circulating blood could produce sufficient pulmonary edema to be a factor in the course of pulmonary tuberculosis and a stumbling block to the cure of this disease. It could also be postulated from known facts concerning the role of the serum proteins in maintaining normal fluid equilibrium between the vascular system and the pulmonary alveoli, that elevation of the serum protein levels could attract fluids back to the vascular system and thereby dehydrate an edematous lung and make tuberculous spread more difficult.

Therefore, the whole question of the relationship of serum protein levels to the progress of pulmonary tuberculosis seemed well worth investigating, and a study was started early in 1948 for the purpose of answering the following questions:

1. Can we demonstrate consistently an alteration of the serum protein levels and of the calculated osmotic pressures in patients with pulmonary tuberculosis?
2. If there is an alteration, is it in proportion to the severity of disease?
3. Can the serum protein levels in a patient be influenced by intravenous plasma, or by the oral administration of protein hydrolysates?
4. Does high protein therapy influence the clinical course of pulmonary tuberculosis?

The present report has to do with the first two questions.

METHODS

Clinical classification and selection of patients.—

The patients were classified by roentgenogram findings according to the standards of the National Tuberculosis Association into minimal, moderately advanced, and far advanced tuberculosis; and according to their clinical status, into A, B, C, and D groupings, group A indicating patients with no apparent symptoms of illness, and group D representing those critically ill. The clinical status was based on such items as temperature, pulse, weight loss, appetite, expectoration, and positive or negative sputum findings. The classification of each patient was reviewed at least every six months, and for the purpose of this study those patients were excluded who had complicating diseases such as severe diabetes, nephritis, or nephrosis. The classification of the 152 patients comprising the study group is given in Table I.

TABLE I. SANATORIUM PATIENTS STUDIED SHOWING THE NUMBER IN EACH CLINICAL CLASSIFICATION*

	STAGE OF TUBERCULOSIS			
CLINICAL STATUS	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL
A	0	3	0	3
B	11	51	15	77
C	0	18	31	49
D	0	4	19	23
Total	11	76	65	152

*According to National Tuberculosis Association definitions.

There are small numbers of patients in some of the groups, as would be expected by the definitions. There were no patients in the classifications of minimal A, C, or D, or far-advanced A. The more significant results could be expected in the groups with the larger numbers of patients.

Total protein and albumin determination.—

Blood was obtained from the patients before breakfast, by venipuncture, and allowed to clot. The serum was separated and cleared of cells. Care was used to avoid color due to hemolysis. The precipitation method described by Reimer[4] was used to determine total serum protein and albumin. In brief, this method consists of separation of globulin by 50 per cent saturation with ammonium sulphate. The albumin remaining in solution, and diluted whole serum, are treated similarly for determination of serum albumin and total protein, respectively. The precipitate obtained by treatment with sodium tungstate and sulfuric acid is redissolved, and color developed in the solutions with Folin's phenol reagent. Comparison with suitable tyrosine standards is made in a DuBoscq colorimeter, and the results calculated to express total protein or albumin in grams per 100 ml. of serum. The globulin values and albumin-globulin rations were calculated from the figures for total protein and albumin.

It is recognized that there are inherent inaccuracies in protein determinations by precipitation methods. For instance, part of the globulin is not precipitated, resulting in albumin values higher than the true values. We were particularly concerned with the reproducibility of our results, and therefore, as a consistency check, a sample of a pool of supposedly normal serum was included in each run. Table II shows representative results with these pooled sera.

TABLE II. REPRODUCIBILITY OF METHOD: RESULTS OF REPEATED TOTAL PROTEIN AND ALBUMIN DETERMINATIONS ON POOLED SERUM

POOL NO.	NO. OF TESTS	RANGE	MEAN	STANDARD DEVIATION	STANDARD ERROR	COEFFICIENT OF VARIATION (PER CENT)
		Total Protein				
I	6	7.39-7.88	7.56	.13	.05	1.7
II	8	7.20-7.58	7.41	.14	.05	1.9
IIIA	4	7.10-7.20	7.13	.05	.03	0.7
V	8	6.78-7.10	6.96	.13	.05	1.9
		Albumin				
I	6	4.94-5.12	5.04	.07	.03	1.4
II	8	5.00-5.25	5.17	.10	.04	1.9
IIIA	4	4.72-5.10	4.93	.15	.08	3.0
V	8	4.54-4.91	4.89	.17	.06	3.7

As noted in the table, the standard error of the mean was no greater than 0.05 for the total protein results, and varied from 0.03 to 0.08 for the albumin figures. Based on mean values, the total protein levels for the four lots of pooled sera ranged from 6.96 to 7.56. The mean albumin values ranged from 4.89 to 5.17, and the globulin (obtained by subtraction) from 2.07 to 2.52. In comparison, Reimer[4] gives normal values of 6 to 8 for total protein, and 4.5 to 5.0 for albumin.

Calculated osmotic pressure.—

Illustrative of the effect of variation of the protein components of serum on colloidol pressure, osmotic pressures were calculated for the mean values for the different groups of patients. The formula used was that of Scatchard, Batchelder and Brown,[5] as modified by Scatchard, given by Poppenheimer and Soto-Rivera:[6]

$$= \frac{268\ (1 - 0.64\ g)\ c}{1 - (0.4 + 0.9\ pH)\ c}$$

= protein osmotic pressure in mm. of mercury.
c = total protein in Gm. per ml.
g = ratio of globulin to total protein.
Factor of conversion of osmotic pressure from mm. of mercury to mm. of water = 13.56.

EXPERIMENTAL DATA

In order to have an over-all picture of the results in the study group, the serum protein findings, albumin-globulin ratios, and calculated osmotic pressures are given in Table III, expressed as average values for the patients in the various roentgenogram classifications and clinical groupings.

In the four tables which follow, the results given in Table III are broken down to show the averages for each type of determination.

TABLE III. SERUM PROTEINS IN PATIENTS WITH PULMONARY TUBERCULOSIS TABULATED ACCORDING TO N.T.A. CLASSIFICATION OF STAGE AND CLINICAL STATUS OF THE DISEASE

NUMBER OF PATIENTS	CLASSIFICATION AND GROUP	SUMMARY OF AVERAGES, IN GM. PER 100 ML.			A/G RATIO	OSMOTIC PRESSURE (CALCULATED)
		TOTAL PROTEIN	ALBUMIN	GLOBULIN		
11	Minimum—B	6.96	4.45	2.51	1.77	382
3	Mod. Adv.—A	7.43	4.83	2.60	1.86	440
51	Mod. Adv.—B	6.81	4.25	2.56	1.66	364
18	Mod. Adv.—C	6.90	4.19	2.71	1.60	367
4	Mod. Adv.—D	6.51	3.53	2.98	1.27	310
15	Far Adv.—B	6.72	4.18	2.54	1.71	352
31	Far Adv.—C	6.79	4.00	2.79	1.49	348
19	Far Adv.—D	6.24	3.54	2.70	1.34	292

Total serum protein.—

The results of the total protein determinations are summarized in Table IV. An average is given for each group.

The findings suggest a slight decrease in the total protein as the disease progresses. Note, for example, the results in group B in which the average for the minimal classification was 6.96; for the moderately advanced, 6.81; and for the far advanced, 6.72. In the far-advanced group, the averages for the B, C, and D classifications were, respectively, 6.72, 6.79, and 6.24. While the variations are not large, the lowest findings appear to be associated with the poorer clinical condition and not necessarily with the stage of tuberculosis.

Serum albumin.—

The results of the determinations for serum albumin are summarized in Table V, each figure being the average for the group.

TABLE IV. TOTAL SERUM PROTEIN IN 152 PATIENTS WITH TUBERCULOSIS, ACCORDING TO THEIR CLINICAL CLASSIFICATIONS

CLINICAL STATUS	STAGE OF TUBERCULOSIS			
	MINIMAL (11)	MODERATELY ADVANCED (76)	FAR ADVANCED (65)	AVERAGE OF GROUP (152)
A (3)	--	7.43	--	7.43
B (77)	6.96	6.81	6.72	6.82
C (49)	--	6.90	6.79	6.84
D (23)	--	6.51	6.24	6.29
Average of group	6.96	6.84	6.61	6.75

The figures suggest relatively greater alterations in the albumin than in the total protein. Here, again, the clinical condition appears to be a more important determining factor in the lower results than does the stage of disease. For example, in the moderately advanced group comprising 76 patients, the respective average albumin determinations for classifications A, B, C, and D are 4.83, 4.25, 4.19, and 3.53 Gm. per 100 ml. of serum. In the far-advanced group of 65 patients there is a corresponding progressive lowering of the albumin level in classifications B, C, and D; namely, 4.18, 4.00, and 3.54 Gm. per 100 ml. of serum, respectively.

TABLE V. SERUM ALBUMIN IN 152 PATIENTS WITH TUBERCULOSIS, ACCORDING TO THEIR CLINICAL CLASSIFICATIONS

CLINICAL STATUS	MINIMAL (11)	MODERATELY ADVANCED (76)	FAR ADVANCED (65)	AVERAGE OF GROUP (152)
A (3)	--	4.83	--	4.83
B (77)	4.45	4.25	4.18	4.27
C (49)	--	4.19	4.00	4.08
D (23)	--	3.53	3.54	3.54
Average of group	4.45	4.22	3.91	4.11

Albumin-globulin ratios.—

The albumin-globulin ratios are of considerable interest. As a basis for calculating these ratios, the average figure for the albumin was subtracted from the average for the total protein to obtain an average for globulin in each group. The ratios of these mean values are given in Table VI.

From the tabulated results it appears that relatively lower ratios are associated with a poor clinical condition, and also, but somewhat less regularly, with the more advanced stages of the disease. The ratios of the 76 patients in the moderately advanced group show a downward trend through the various classifications, that is, 1.86, 1.66, 1.54, and 1.18 for A, B, C, and D, respectively. In the far-advanced group the ratios show the same general downward tendency

TABLE VI. ALBUMIN-GLOBULIN RATIOS IN PATIENTS GROUPED ACCORDING TO THEIR CLINICAL CLASSIFICATIONS

CLINICAL STATUS	MINIMAL (11)	MODERATELY ADVANCED (76)	FAR ADVANCED (65)	TOTAL (152)
A (3)	--	1.86	--	1.86
B (77)	1.77	1.66	1.64	1.68
C (49)	--	1.54	1.44	1.48
D (23)	--	1.18	1.31	1.29
Total	1.77	1.61	1.45	1.56

in the more critically ill patients. Here we note the ratios to be 1.64 1.44, and 1.31 in the classifications B, C, and D, respectively.

Calculated osmotic pressures.—

Using the formula of Scatchard referred to under *Methods,* the osmotic pressures for the average albumin and globulin values for the different classifications were calculated. These are given in Table VII.

These figures illustrate the effect of lowered serum protein, especially lowered albumin, on the osmotic pressure of serum. The average values for groups A, B, C, and D are 440, 364, 356, and 296, respectively. Similarly for the minimal, moderately advanced, and far-advanced groups the respective values for osmotic pressure are 382, 362, 334.

TABLE VII. CALCULATED OSMOTIC PRESSURES OF SERUM IN PATIENTS GROUPED ACCORDING TO ROENTGENOGRAM AND CLINICAL FINDINGS

CLINICAL STATUS	STAGE OF TUBERCULOSIS			
	MINIMAL (11)	MODERATELY ADVANCED (76)	FAR ADVANCED (65)	AVERAGE OF GROUP (152)
A (3)	--	440	--	440
B (77)	382	364	352	364
C (49)	--	367	348	356
D (23)	--	310	292	296
Average of group	382	362	334	350

Serum protein levels in dying patients.—

The serum protein levels of patients dying of pulmonary tuberculosis during the course of the study are shown in Table VIII.

In most of these patients very low serum protein levels are observed. The albumin and albumin-globulin ratios are also low, and consequently the osmotic pressures. These findings in patients shortly before death support the observation that the serum proteins vary in proportion to the severity of the disease.

TABLE VIII. SERUM PROTEIN LEVELS OF 15 PATIENTS DYING OF PULMONARY TUBERCULOSIS

PATIENT	INTERVAL BETWEEN TEST AND DEATH	TOTAL PROTEIN	ALBUMIN	GLOBULIN	A/G RATIO	OSMOTIC PRESSURE
A.A.	2 Days	6.70	2.95	3.75	0.79	297
D.C.	1 Month	6.39	3.50	2.89	1.21	300
E.D.	1 Month	3.72	1.82	1.90	0.96	123
G.F.	2 Months	6.62	3.72	2.90	1.28	324
J.G.	4 Days	6.85	2.98	3.87	0.77	308
C.H.	2 Months	5.41	2.91	2.50	1.16	224
R.H.	1½ Months	5.76	3.56	2.20	1.62	268
F.M.	6 Months	6.22	3.17	3.05	1.04	277
C.M.	11 Months	5.38	3.06	2.32	1.32	228
H.M.	6 Months	6.10	3.80	2.30	1.65	296
E.S.	5 Months	6.78	3.86	2.92	1.32	344
S.S.	1 Month	6.74	3.50	3.24	1.08	322
G.T.	3 Months	6.13	3.75	2.38	1.58	295
W.V.	3 Months	5.74	3.49	2.25	1.55	263
J.V.	4 Months	6.15	3.05	3.10	0.98	268

DISCUSSION

For an understanding of the physiology involved, we need to recall that the serum proteins are responsible in large degree for the colloid osmotic pres-

sure which regulates fluid equilibrium between the vascular system and the tissues. In this connection the discussion by one of the authors[7] in relation to lowered serum proteins associated with spinal cord edema in poliomyelitis is relevant. Of the serum proteins, the albumins are the smallest molecules and are the most copious. In normal plasma, the albumins make up over 60 per cent of the protein constituent and, according to several physiologists, including Best and Taylor,[8] they are responsible for nearly 80 per cent of the colloidal osmotic pressure exerted by the plasma. Therefore, any appreciable change in the albumin content of the plasma will have an immediate effect upon the osmotic pressure which this plasma is capable of exerting. Loss of positive osmotic pressure as a result of a reduction of the albumin content, in which there is usually a reversal of the albumin-globulin ratio, will induce a transudation of the small albumin molecules, as an albuminous fluid, to the tissues and into the alveoli. Such decrease in serum albumin caused either by accelerated protein catabolism or disturbed protein synthesis and occurring as one of the systemic manifestations of disease, would lower the plasma osmotic pressure and accentuate the edema of the lung. Conversely, if the serum albumin and osmotic pressure were raised, the process might be reversed; the lung might become less moist and less likely to encourage the spread of the disease tuberculosis. The findings would seem to justify further experiments directed towards raising the albumin level and hence the osmotic pressure, by intravenous plasma or the oral administration of protein, and a study of the effect of such an alteration on the clinical course of the disease.

SUMMARY AND CONCLUSIONS

The results of serum protein studies in 152 patients with pulmonary tuberculosis have been reported.

The most significant alteration appeared to be in the serum albumin fraction, and, in general, it was found that the more severe the disease, the lower was the albumin level.

It is believed that serum protein levels deserve greater attention in the evaluation of pulmonary tuberculosis. Further studies are in progress to investigate the value of intravenous plasma and oral protein hydrolysates in the therapy of selected tuberculous patients.

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BRONCHIAL ADENOMA*

Nomenclature and Present Methods of Treatment

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BRONCHIAL adenoma has been recognized for many years. In 1937, for the first time, Zamora and Schuster[1] reported an adenoma which presented evidence of malignancy by local invasion. By 1943 several cases of distant metastasis,[2, 3, 4] picked up microscopically and incidentally, were reported. In 1943, Anderson[5] reported a macroscopic metastasis to the liver. Gordon[27] reported removal of the left lobe of the liver for tumor identical with a bronchial adenoma removed earlier in the same patient. Similar reports[6] followed. Adams[25] reports death due to cerebral metastases in a woman known also to have liver metastases from bronchial adenoma. From the time of the initial report in 1937 to the present time there has been discussion as to whether these tumors are benign or malignant. Since the lesion is relatively uncommon, facts which have become known about it have been disseminated only slowly. Generally, treatment has not varied a great deal because those not treated initially by surgery usually come to surgery later as a result of complications. A point we would like to make is that surgical resection, or at least exploration, is generally indicated as primary therapy for these tumors. It is commonly accepted that they are not of a degree of malignancy to be compared with that of bronchiogenic carcinoma, but some still deny that they are malignant at all.[7] As the subject continues to be one for study, efforts are being made to correlate clinical course with pathologic findings, and to try to establish some concrete basis on which to determine what treatment of these should be.

One opinion as to the origin of these tumors is that they arise from glands of the bronchial mucosa. Stout[9] and Haemperl[10] demonstrate certain cells in these glands by special staining which they call "Onkocytes." These they believe to be the source of bronchial adenoma. Womack and Graham,[3] and Harris and Schlattenberg[11] feel that the tumors are due to persisting embryonal bronchial buds. A resemblance to fetal lung tissue is noted by Churchill,[12] who suggests that they are vestigial pulmonary lobes growing within the bronchus. Similarity of some of the tumor cells to lymphocytes has been described by certain authors[13] who proposed that to such tumors the term lymphoid or angiolymphoid be applied.

Only one hypothesis in the discussion of possible sources of these tumors seems to be accepted with something approaching unanimity of opinion: these tumors, though considered to be epithelial, are separated character-

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istically from the surface epithelium of the bronchus, and it would appear that they do not take their origin from the surface epithelium, but probably from bronchial glands.[5, 14-18]

Clinically, the symptoms resulting from bronchial adenoma can be ascribed in the majority of cases to complication more frequently than to the tumor directly. Cough, hemoptysis, and expectoration are common, but probably arise because of a condition brought about by the obstruction of the bronchus—atelectasis, bronchiectatic changes, and so on. Pneumonia, pleurisy, or even empyema may be the presenting clinical picture, or the patient may complain of mild chest pain, dyspnea, fever, weight loss, or wheezing. Severity of symptoms will depend for the most part on severity of the secondary conditions, and these will be influenced as much by the location of the tumor as by its size. Physical findings will be conspicuous by their absence unless secondary

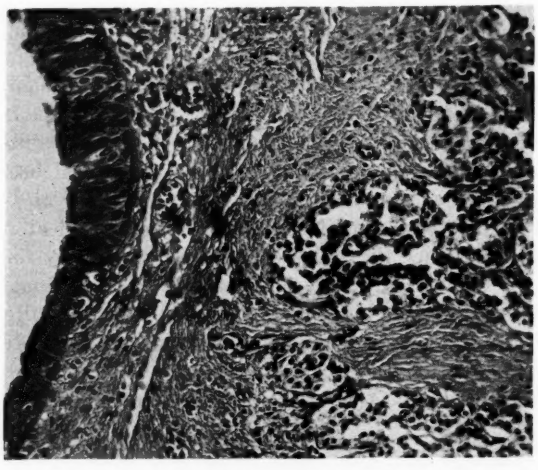

Fig. 1.—Carcinoid adenoma (×200), showing relationship to bronchial epithelium.

developments have appeared, in which case the findings will be those of the secondary condition. This is worthy of emphasis because cases may go undiagnosed because of a paucity of findings or because bronchial adenoma is not suspected. Treatment without proper diagnosis may thus be unnecessarily prolonged. In reported cases treatment for bronchiectasis, pulmonitis, and so on, has extended over long periods before bronchial adenoma has been suspected as the underlying cause.[19] Certainly, in some of these cases early removal of the source of the obstruction might be expected to relieve the condition before irreparable damage has occurred.

Abnormalities demonstrable by roentgenogram[20] include: demonstrable tumor, atelectasis, inflammatory infiltration, or any combination of these. In one report the only finding was unilateral emphysema in expiration, due to a ball-valve type of obstruction. The routine roentgenogram of the chest was

normal. In the series of cases reported by Holly,[18] a tumor was visible in 20 per cent, atelectasis in 40 per cent, and inflammatory infiltration in 23 per cent. Tumor was not demonstrable by roentgenogram in any of the cases included in this report.

Bronchoscopically, the tumor appears as a smooth, red, rounded tumor, usually with a broad base. Bleeding appears with minimal trauma, and at times may be a source of considerable discouragement when biopsies may be desired. Tendency to bleeding of serious proportion is shown by reported cases in which death has resulted from massive blood loss and shock,[22, 23, 24, 42] or the patient drowned in his own blood when the respiratory passages were suddenly inundated. The majority of bronchial adenomas occur in the primary passages, and they seem to be more frequently located in the right main lower lobe bronchus. With a tumor located in this position prolonged bronchoscopic treatment and observation may be enticingly convenient.

The presence of such a lesion, of course, requires biopsy for diagnosis. The pathologist also has his problem with these tumors. Without, for the moment, going into the pathologic ramifications, it may be said that not infrequently it is very difficult to distinguish some of these from small, round-cell carcinomas of the bronchus, which are highly malignant. Many instances have been reported in which distinction has been made only on subsequent review of the section or after a patient's clinical course failed to corroborate the prognosis. On frozen section in many of these, such differentiation is virtually impossible. This should give further impetus to efforts directed toward clarification of characteristics of these tumors and toward attainment of a common ground of understanding regarding them, for a decision made during exploratory thoracotomy may be greatly influenced if this fact is borne in mind. An adenoma with mediastinal metastases would probably offer an excellent opportunity for cure, whereas a small, round-cell carcinoma with such metastases would probably not justify even an attempt.

The following case reports will illustrate several points we feel should be emphasized:

CASE REPORTS

CASE 1.—P. H. D., a 25-year-old white man, was admitted on Nov. 14, 1942, with a complaint of hemoptysis of about half a cup of blood daily for about a week. A month prior to this he had had bronchopneumonia. After discharge from the hospital he noticed a "tickling in the throat," and on coughing and clearing his throat he would bring up one or two teaspoonfuls of bright blood. The cough was otherwise nonproductive. There had been weight loss of twenty pounds in the period preceding the present illness, but this was felt to be related to factors other than his physical illness. Physical examination was not remarkable except for a tiny ulcer found on one of the vocal cords. Bleeding was considered not to be coming from this. Bronchoscopy disclosed a tumor in the left lower bronchus which bled on slightest instrumentation. Frozen section was interpreted as "Oat-cell Carcinoma of the Bronchus," but when permanent sections were examined the diagnosis was changed to "Benign Adenoma of the Bronchus." On Dec. 1, 1942, the tumor was removed locally through the bronchoscope. Healing was rapid and satisfactory. A month later slight fullness was visible at the site. Four months later this had progressed, and it was apparent that the tumor was still present. In August, 1943, it was again removed through the

bronchoscope at Memorial Hospital in New York. In November, 1943, it was once more visible and was cauterized through the bronchoscope. There was no further trouble until early 1948 when further symptoms developed. In May, 1948, a pneumonectomy was performed at the Ochsner Clinic. Since that time the patient has been well except for minor dyspnea on exertion. In this case resection was undertaken after five years of prolonged bronchoscopic treatment and observation. It would appear that the final result could have been achieved five years earlier if surgical exploration had been carried out.

CASE 2.—H. K. M., a 37-year-old white man, was admitted in March, 1949, complaining of persistent, mild, relatively nonproductive cough. There were no other symptoms, and general health was good. There had been no weight loss. Chest roentgenogram showed atelectasis of the right middle lobe, but repeated studies failed to disclose the cause of the atelectasis. It was felt that bronchogenic carcinoma was the most likely possibility. The patient refused operation. On Sept. 6, 1949, he returned with the same picture, which had persisted unchanged. General condition remained good. On Sept. 10, 1949, the right middle lobe was removed. A frozen section was interpreted as small, round-cell carcinoma, and total pneumonectomy was done. Enlarged hilar nodes were found and removed. The patient made a good recovery, and was discharged to his home on Sept. 26, 1949. In December, three months later, he was preparing to return to his regular work. Paraffin section showed the tumor to be bronchial adenoma of the carcinoid type. Three nodes were removed, which were not contiguous to the bronchus; these contained tumor which duplicated the pattern of that found in the parent growth. Here metastasis had occurred even with relatively short clinical duration of illness. At surgical exploration it was possible to remove nodes already containing tumor which might never have been resectable after bronchoscopic removal of the parent growth followed by prolonged observation.

CASE 3.—W. K. K., a 27-year-old white man, was admitted July 30, 1947, with a history of fever, nonproductive cough, anorexia, and vomiting for five days. He developed pain in the right chest which was aggravated by breathing, and on the day prior to admission had dyspnea and slight cyanosis. On admission a diagnosis of lobar pneumonia of the right lower lobe was made, with overlying pleurisy. This was confirmed by roentgenogram, but remark was made that there was a large atelectatic factor. On Aug. 6, 1947, bronchoscopy disclosed a mass which bled very easily, obstructing the right lower lobe bronchus. Frozen section of the biopsy was diagnosed as small, round-cell carcinoma. Later, permanent sections were interpreted as "Malignant Adenoma." On Aug. 14, 1947, a right pneumonectomy was performed when it became evident that the tumor not only filled the lower lobe bronchus but was also encroaching upon that of the right middle lobe. Several hilar nodes were removed but showed no tumor. The patient was discharged Sept. 15, 1947, in good general condition. The final pathologic report was "Bronchial Adenoma, with involvement of two contiguous peribronchial nodes." Bronchiectasis and pneumonitis were also present. In November, 1949, the patient reported that he had morning cough with which he brought up a considerable amount of "phlegm." He had had no significant cough thereafter during the day. This might indicate some mild bronchiectatic process in the opposite lung. It points up the danger of delay in treatment which may permit infection to become established in the opposite lung. The case demonstrates again that removal without surgical exploration is not adequate. Routine chest roentgenogram was clear in August, 1949.

CASE 4.—C. W. H., a man in his late forties, was admitted in May, 1944, for repair of a small right inguinal hernia. On questioning, he remarked that it had developed because of a bad cough he had had for about a year. Chest studies were carried out, and he was found to have complete obstruction of the left lower lobe bronchus with atelectasis of the lobe. Biopsy was interpreted as "Basal-cell Carcinoma, probably arising in a benign adenoma." A left pneumonectomy was carried out, the patient made a very satisfactory recovery. The operative specimen showed a tumor 4 cm. in diameter in the main bronchus of the left lower

lobe. No metastases were evident, but there was an extensive infiltration through the bronchial wall into surrounding lung tissues. The patient, at the time of this writing, is progressing very satisfactorily. He weighs approximately fifteen pounds more than he did prior to the operation. There is a mild residual cough, believed to be associated with accumulation of secretion in the blind bronchial stump. Dyspnea is present only on exertion and is surprisingly little. On review of the sections this tumor was found to fall into those which we call the mixed tumor group, also called, among other things, adenocystic basal-cell carcinoma of the bronchus, or cylindroma. This type is considered by many to be more malignant, metastasizing more frequently than the carcinoid type.

Until 1937 little question was ever raised regarding the supposedly benign nature of these lesions, and major surgical procedures were undertaken only when necessitated by complications. Since then the various improvements in surgical techniques and methods of treatment and the continual reports indicating malignant characteristics in these lesions have aroused in many the feeling that surgical exploration, usually with resection, should be the preferred method of treatment. Secondary factors or unassociated conditions may, of course, interfere with the carrying out of the most desirable therapy.

The relatively few tumors not accessible to bronchoscopic instruments must be treated by other methods. Since the majority are in the primary passages and are commonly in the lower lobe bronchi, however, there is some choice. They may be subjected to biopsy, fulguration, desiccation and cauterization, or, rarely, excision through the bronchoscope. In 1940, Eloesser[29] reported the use of posterior bronchotomy as a means of approaching and removing these tumors without sacrificing the lung. This was again mentioned in 1947 by Goldman,[30] as being used in one case. Langston and Fox,[31] in 1948, described a technique of posterior bronchotomy for the treatment of this condition, but emphasized that such approach is limited in its use and is possible only in selected cases. Lobectomy may offer the best attack, and pneumonectomy will be necessary in some. Complicating infection may prevent treatment directed toward the tumor itself.[19] In some instances a combination of types of treatment may be called for. Recurrence after bronchoscopic removal should be sufficient indication for surgical exploration and resection, if possible. Inability to remove a tumor surgically would call for palliative measures by the bronchoscopic route. The bronchoscope may permit relief of obstruction, evacuation of suppurative material, and may at times allow preservation of some of the pulmonary tissue in subsequent removal of the tumor at surgical exploration.

Series have been reported to support the views of those favoring bronchoscopic treatment,[32] and others to support the views of those favoring exploration and resection. It must be admitted that statistical differences are not striking.[32] This is not remarkable, however, for the tumors are slow-growing, metastasize only occasionally, according to present reports, and five-year cures would be an unsatisfactory criterion. On the other hand, the stanchest of those claiming these tumors to be benign admit that they invade locally, invasion of the bronchial wall being considered characteristic.[34] Extension to

the mediastinum is admitted generally, although some feel this is simple extension, while others consider it often frank metastasis. In 1945 Moersch, Tinney, and McDonald[35] stated: "We have never seen a case with metastasis, and this ultimately distinguishes between this ('adenoma'—'cylindroma' not included) and bronchogenic carcinoma." Van Hazel, Holinger, and Jensik[36] conclude that "adenomas" are extremely slow-growing and locally invasive, whereas the "cylindromas" "met all the criterion of malignant neoplasm."

The former group reported six cases of "cylindroma" with the opinion that these resemble mixed tumors and present a different appearance from "Adenoma of the Bronchus." Others, however, feel that all these tumors can only be considered as one group—adenoma. Holly,[18] in reporting thirty-nine cases, felt that it was possible to distinguish two groups, the "Carcinoid" and the "Mixed Tumor Type." Laff and Neuberger[37] recognized those with a "carcinoid-like" pattern and those with a "cylindromatous" pattern. However, both groups described by Laff and Neuberger are included in one group by others, and the "cylindroma" described by some falls into the mixed tumor group of Holly.

Such confusion tends to disorganize any concerted attempts at clarification and certainly would discourage many of those more likely to be concerned with the early recognition of the condition and generally the early treatment of the average case—the general practitioners.

There are objections to be raised to most of the terms already in use. Carcinoid has long been applied to tumors of the appendix and the gastrointestinal tract which show argentaffine granules. Tumors of the bronchus which resemble these morphologically have not shown such granules except in isolated and unconfirmed instances. Carcinoid-like was coined by one group to circumvent this, but seems redundant. "Adenoma" is a term which has long been applied to these tumors as a whole, and to the average medical group continues to mean just that. To take this term and apply it now to certain types as distinguished from others in the same category is to bring about more misunderstanding. The term cylindroma, which at present seems widely in favor, has brought possibly more confusion than any of the others.[5] One attempting to study these growths must, of necessity, familiarize himself with what is meant in each case when the term is used, but if further knowledge in the field is to be disseminated, consistency must be maintained. According to Dorland's Medical Dictionary, a cylindroma is a tumor in which the *stroma* has the form of elongated, twisted cords of hyaline material. According to the caption of a photograph accompanying a recent article on the subject[36] the cylindroma (bronchial) is one in which the "acini" are likened to "cylinders." It is the concept of the cylindroma as described by these authors which seems to be most commonly held. Again, in *Anderson's Pathology*[38] "The term cylindroma refers to the hyaline tubes and cylinders of the stroma." Similarity of the "cylindroma" to epithelioma adenoides cysticum has been noted. According to Menetrier, in 1927,[39] Billroth was the first to apply this term, and did so

when a tumor which was squeezed produced rounded long masses which he thought resembled cylinders. In 1932, Stout[40] stated: "The term cylindroma is no longer used, and rightly so; because it describes simply a morphological variation and not an entity. The mucinous "cylindromas" should be called mixed tumors; the hyaline "cylindromas" (skin) should be called basal-cell

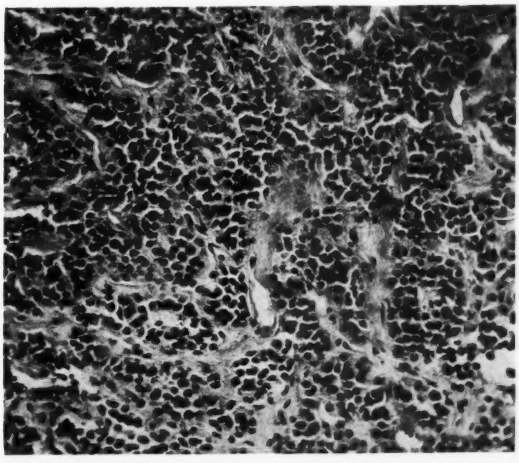

Fig. 2.—Carcinoid adenoma (×200).

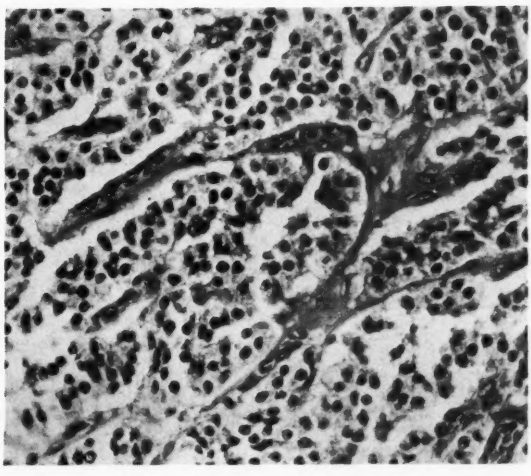

Fig. 3.—Carcinoid adenoma (×400).

epitheliomas." It would be wise to return to the evaluation of the term, and to discard it. Yet further confusion should not be introduced by further coining of new names.

If two distinct classes are to be described it would seem that they might well be characterized as the "Carcinoid," with the understanding that the bronchial "carcinoid" has not been found to show argentaffine granules, and those described as "mixed tumors," which group would include the "cylindromas." This will not be in disagreement with most authors. Moersch, Tinney, and McDonald,[35] for instance, in referring to the "cylindromas," "these resemble mixed tumors . . ." The term "adenoma" should be reserved for application to the group as a whole.

In the carcinoid adenoma, the cells are characteristically arranged on a branching and interlacing network of moderately cellular connective tissue so that cleftlike and branching spaces are noted between the cell groups. The individual cells show a moderate amount of very finely granular eosinophilic cytoplasm. The nucleus is slightly hyperchromatic, round or oval, and usually centrally placed. There is some variation in size of the nuclei, but this is not extreme or characteristic. Nuclear chromatin is diffusely arranged in a finely reticular network. Density varies, and in some areas the stroma may predominate so that adenoma cells occur compactly in groups of small number,

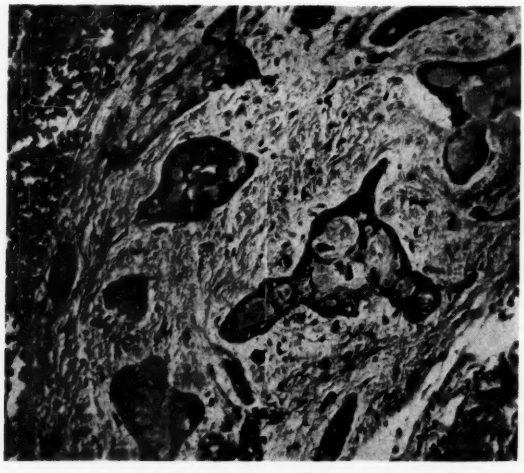

Fig. 4.—Mixed tumor adenoma (×200).

and no spaces are seen. In other areas adenoma cells are predominant so that they appear in anastomosing cords, again with no definite spaces. Mitoses are rare or absent. The pattern is closely similar to that of carcinoid tumor found in the bowel.

The cells of the mixed tumor adenoma are arranged in branching tubular masses or as circumscribed rounded groups, sometimes with "palisading" of those peripherally placed. Within the various groups there are inconsistent irregular spaces which often contain "mucinous" material. (This does not

always stain with mucicarmine.) Those that have a round lumen and are lined by cuboidal cells bear a striking resemblance to the ducts of the mucinous glands found in the oral and nasal cavity and in portions of the respiratory tree. This suggests origin of this tumor in small ducts. The branching tubular arrangement may isolate round, circumscribed areas of the stroma. The cell outline is polygonal, conforming to contiguous cells. Cytoplasm is scant to moderate, and palely eosinophilic. Nuclei are generally rounded or oval, but may be irregular or elongated as if to conform to pressure of ad-

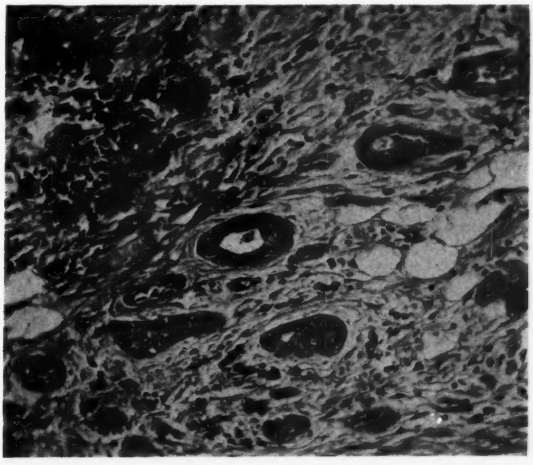

Fig. 5.—Detail of Fig. 3 (×400). Note resemblance to ducts and presence of anthracotic pigment.

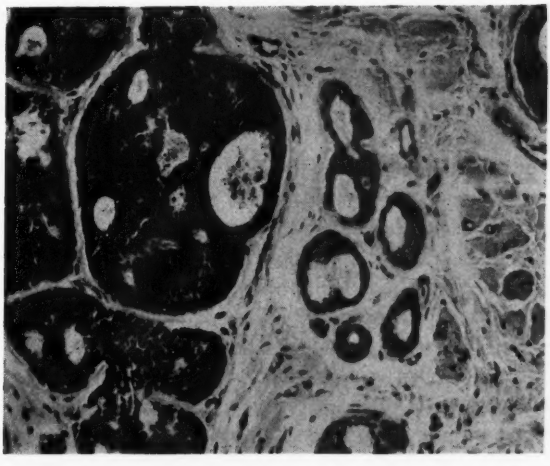

Fig. 6.—Adenocystic basal cell carcinoma from oral cavity (×200). Note histologic resemblance to mixed tumor adenoma of the bronchus.

jacent cells. Nuclear chromatin is hyperchromatic, rather coarse. One moderate-sized nucleolus is usually present. The stroma varies. It is sometimes dense with sweeping collagenous bundles enclosing small scattered groups of tumor cells, or it may be loose, almost myxomatous in appearance, and comprise only a minor proportion of the mass. Bone, cartilage, and fat have been reported in these tumors, but none was noted in our cases.

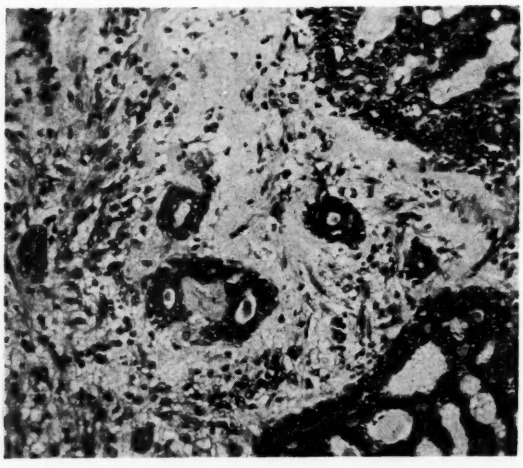

Fig. 7.—Adenocystic basal cell carcinoma of maxillary antrum (×200). Note resemblance to mixed tumor adenoma of bronchus.

Since disagreement exists as to which of these shows tendency of greater or lesser degree to metastasize, it is imperative that a generally accepted system of nomenclature be used, if the question is to be resolved. Van Hazel, Holinger, and Jensik[36] conclude that adenomas (carcinoid adenoma) are relatively benign, whereas cylindromas (mixed tumor adenoma) are malignant. On the other hand, Holly's series[18] of cases contained a number of the carcinoid type which showed distant metastasis. One of the cases here reported is that of a carcinoid adenoma with definite metastasis to the mediastinum; another had metastasized or extended, according to one's viewpoint, to nearby peribronchial nodes. Other cases have been reported of distant metastasis of carcinoid adenoma. Recently a case has been reported in which death was ascribed to the direct effects of metastases of bronchial adenoma,[25] and Cheek and Muirhead, in 1948,[41] report a case in which transition from typical bronchial adenoma to alveolar cell carcinoma pattern is described, with widespread metastasis and death. Other cases strongly suggestive of transition of adenomas to carcinomas have been reported.[8, 26] Possibly of more practical significance is the fact that both these tumors, carcinoid or mixed tumor, are known to extend or metastasize to the mediastinum, and are locally invasive. It is this feature which would seem to make surgical removal mandatory by a

means which will permit adequate examination of areas to which the tumor may have spread. Mediastinal tumor will kill simply through its presence and growth whether "malignant" or not, although a patient may survive for years before this occurs. The unhappy lot of a patient with bronchiectasis, fistulae, empyema, recurrent bouts of pneumonia, and such should be kept in mind whenever survival rates are to be compared. Cases reported by Adams and others[2] illustrate the disaster invited through failure of physicians to diagnose the condition sufficiently early to permit adequate therapy.

If the tumor invades at all, then only in exceptional cases will it be possible to remove it bronchoscopically with any reasonable degree of certainty that it has been adequately removed, probably only in those with a small, easily visualized and distinct pedicle. Posterior bronchotomy is applicable, as its proponents indicate, in selected cases and has the advantage of permitting some examination of the mediastinum. In the great majority of cases we feel that surgical exploration with lobectomy or pneumonectomy and removal of mediastinal nodes, where indicated and possible, is the procedure of choice. The malignant propensities of these tumors are becoming more generally recognized as unquestionable instances of metastasis and are reported one after the other, yet one is surprised to realize how great is the lag in general acceptance of recently discovered facts in the case of a fairly uncommon lesion such as these represent. One can hardly expect, however, other professional men to develop concrete opinions regarding these tumors when they remain such a source of disagreement among thoracic surgeons themselves.

As to comparative malignancy, it appears that we are dealing with two types of tumor, possibly representing the same basic tumor, both of which are of low-grade malignancy, both of which are known to invade the mediastinum by metastasis or extension, and both, therefore, carrying similar potentialities with regard to the risk to the patient. It would seem that no purpose is served in distinguishing them at the present time so far as definitive treatment is concerned.

SUMMARY

1. Five cases of adenoma of the bronchus are presented.

2. Attention is called to the confusion resulting from the use of varying and nondescript nomenclature. It is suggested that "Adenoma" be reserved for the group as a whole, that "Carcinoid Adenoma" and "Mixed Tumor Adenoma" be used exclusively in classifying these since they are adequately descriptive terms and have been previously used. The term "Cylindroma" should be discarded.

3. It is pointed out that three, at least, of the five cases reported could not have been properly treated by bronchoscopic instrumentation alone. Nothing less than surgical exploration can offer clear evaluation of the condition and permit definitive treatment because the bronchial adenoma extends or metastasizes peribronchially and to the mediastinum.

4. In any patient suffering from repeated episodes of pulmonary inflammation, chronic cough, hemoptysis, and so on without adequate explanation, bronchial adenoma should be suspected and ruled out.

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BRONCHIAL ADENOMA IN A SUPERNUMERARY TRACHEAL LOBE

Report of an Unusual Case

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BRONCHIAL adenoma is no longer a rarity in the recent medical literature. The increasing diagnostic acumen in the recognition of the bronchial adenomas and their favorable prognosis following surgical removal has certainly been sufficient reason for the large series of case reports in the last decade.[6-8, 12-18]

The case which is to be described here is of interest because of the adenoma involving a supernumerary lobe originating from the lateral wall of the trachea slightly above the orifice of the right main stem (Fig. 5).

CASE HISTORY

W. D., No. 14,186, white male, 32 years of age, was admitted to the Veterans Administration Center Feb. 3, 1950.

Past History.—The patient became ill about ten years ago (Fig. 1), while in service—complaining of chest pains in the right side, nonproductive cough, and blood-streaked sputum. He was hospitalized on seven different occasions for the same complaint prior to entrance to our hospital. Bronchoscopy performed elsewhere in November, 1944, revealed edema and occlusion of the right upper lobe bronchus. There was no air exchange through the lumen of this bronchus. Biopsy report from that area was not conclusive, and exploratory thoracotomy was performed in March, 1945. The following was reported by the surgeon:

"The hilus was fixed and incorporated into a firm, nodular mass which was closely adherent to the pericardium, and thought to be too fixed for removal. This mass was aspirated and found to be firm and homogeneous, and there was no pus or other fluid in the two areas aspirated."

The patient was discharged on Aug. 6, 1945, without much improvement. During the next five years he consulted several physicians without any definite result.

Physical Examination.—Physical examination on present admission revealed a fairly well-developed, slightly undernourished white man who appeared chronically ill. Temperature, pulse, and respirations were within normal limits. Examination of the chest revealed dullness to flatness on percussion with diminished to absence of breath sounds over the upper third of the right chest. There were no râles or wheezing present. The remainder of the lung fields were clear and resonant throughout. The roentgenogram (Fig. 2) revealed a density in the right upper lung field with its lower border sharply delineated at the level of the second anterior rib. Other portions of the lung were well aerated. The trachea, heart, and mediastinum were in normal position.

All the laboratory findings including sputum, as well as electrocardiograph, were not significant. Bronchoscopy showed that the opening of the right upper lobe bronchus originated slightly above the carina. Little attention was paid, however, to this abnormality at the time of the examination. In addition to the above finding, there was also marked stenosis of the upper lobe bronchus with edema and signs of chronic irritation. The biopsy material from the affected bronchus showed again only atypism of the bronchial epithelium without any definite evidence of an adenoma.

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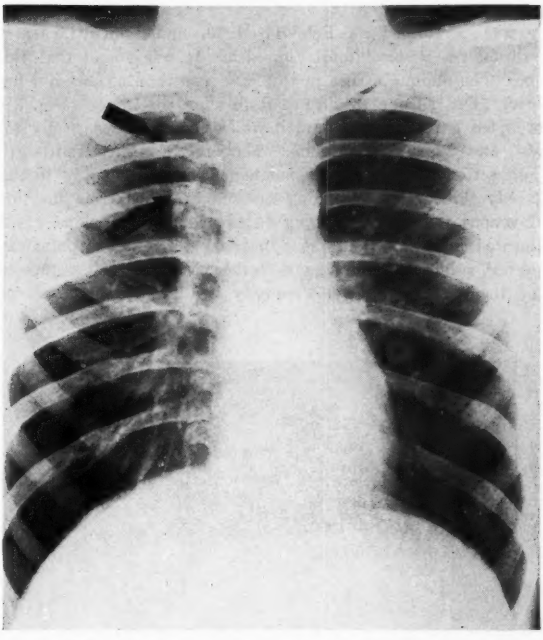

Fig. 1.—Dec. 1, 1941, roentgenogram of the chest showing abnormal density in the right upper lobe as outlined by the two arrows.

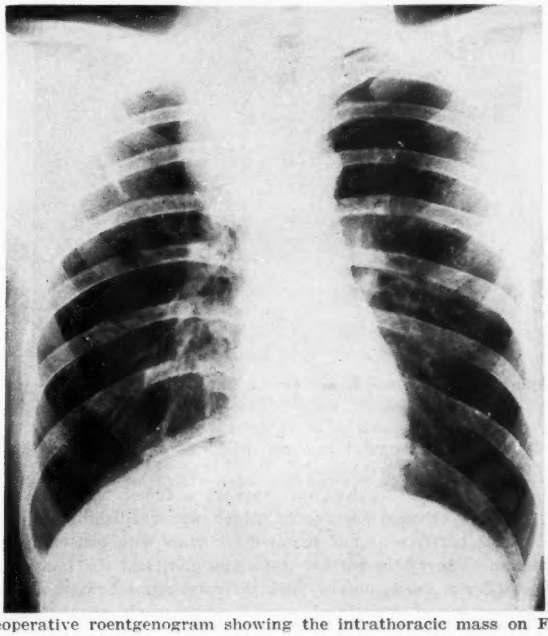

Fig. 2.—Preoperative roentgenogram showing the intrathoracic mass on Feb. 3, 1950.

Thoracotomy was performed on Feb. 14, 1950, under intratracheal gas-oxygen and ether anesthesia, through a posterolateral approach. It was found that this patient had a supernumerary lobe. The oblique fissure in this case was running anterior and the horizontal fissure was posterior to it, as one would see it in a mirror image (Fig. 3). The so-called upper lobe was occupied entirely by a growth which was attached firmly to the chest wall, cupola of the chest, and upper mediastinum. The lung was freed with great difficulty by sharp and blunt dissection from its attachments. The blood supply to the supernumerary lobe consisted of only three short ascending arterial branches from the inferior pulmonary trunk and several venous tributaries running to the superior pulmonary vein. The venous tributaries were located rather deep in the pulmonary tissue. The pulmonary ligament was attached to the anterior lobe, which suggested the possibility of a reversal of the lobes. During removal of the bronchus, it was necessary to diminish the lumen of the trachea to some extent.

Fig. 3.—Photograph showing the horizontal fissure anteriorly and the oblique fissure posterior to it.

The patient made an uneventful recovery, and was discharged on the fourteenth postoperative day.

Pathology.—The specimen removed consisted of a tumor mass measuring 12.5 by 8.5 by 5.5 cm. (Fig. 4), the external surface of which was reddish-brown and shaggy. The pathologist reported "a partly solid and partly cystic mass with scattered areas of small bits of calcified substance. The cystic portion is multilocular, and the individual cysts vary in diameter from 5 to 20 mm., and contain thick yellowish mucoid material lined with a white membrane. The entire tumor is enclosed in a fibrous capsule about 3 mm. in thickness."

The bronchus was distorted, compressed, but not ulcerated by the tumor. The microscopic report (Fig. 5) was as follows: "The tumor is composed of small rounded cells of almost uniform size. The cells are arranged in solid nests, acinar formations, and interlacing festoons. There is present a scanty hyaline fibrous stroma. The tumor involves the wall of the large bronchus and, except for a small area of ulceration, the mucosa is intact over it. The mucosal cells are well differentiated. The capsule proves microscopically to be a pseudo-capsule. There are many compressed bronchi with inflammation in their walls and with patchy ulceration of the mucosa. Fibrosed collapsed pulmonary tissue is also present in the capsule with many blood vessels and nerves. Scattered solid areas resembling intestinal carcinoids are seen. No evidence of metastasis is found in the lymph node. The calcified material noted grossly was not included in the sections." The pathologic diagnosis was: Bronchial adenoma, carcinoid type.

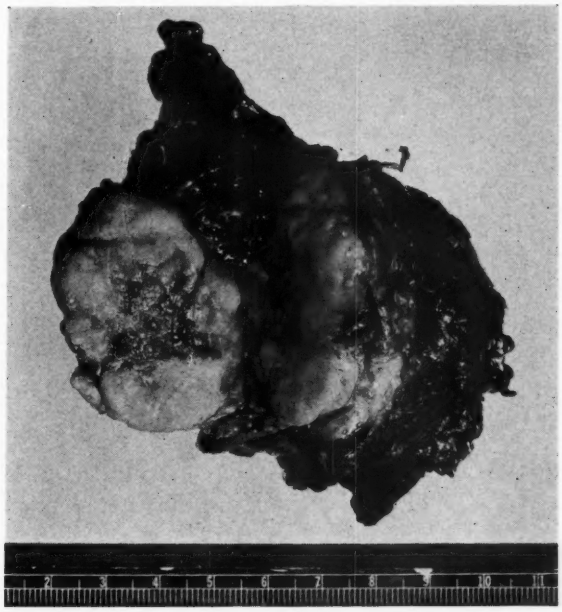

Fig. 4.—Photograph of the excised lobe showing the tumor occupying the entire supernumerary lobe. Observe the multilocular cysts with several small calcified areas in it.

Follow-up roentgenograms with lipiodol study on April 13, 1950, one month after the operation, showed a normal bronchogram of the right lung (Fig. 6). From these films, taken separately after each lobe was filled individually with lipiodol, it was found that the patient still had three separate bronchi connected with lobes on the right side, even after the removal of the so-called fourth lobe.

The patient now has no complaints and is able to follow his present occupation.

DISCUSSION

It is a well-known fact that bronchial adenomas are tumors associated with other abnormalities of the lungs. A thorough search through all pertinent literature failed to reveal a case of similar nature: an adenoma involving a

A. *B.* *C.*

Fig. 5.—*A*, *B*, and *C*, Photomicrographs showing the histology of the tumor and its pseudocapsule.

bronchus which arose from the lower end of the trachea. Graham[19] performed a right pneumonectomy on March 7, 1935, for a mixed tumor arising from the bronchus in the right lower lobe, and during the resection he found several abnormal bronchi connecting the upper lobe directly with the trachea. Overholt,[15] on the other hand, cautions about the possibility of an accessory right upper lobe originating from the trachea which one may find during resections; but no one has formerly reported the presence of a tumor in a supernumerary lobe.

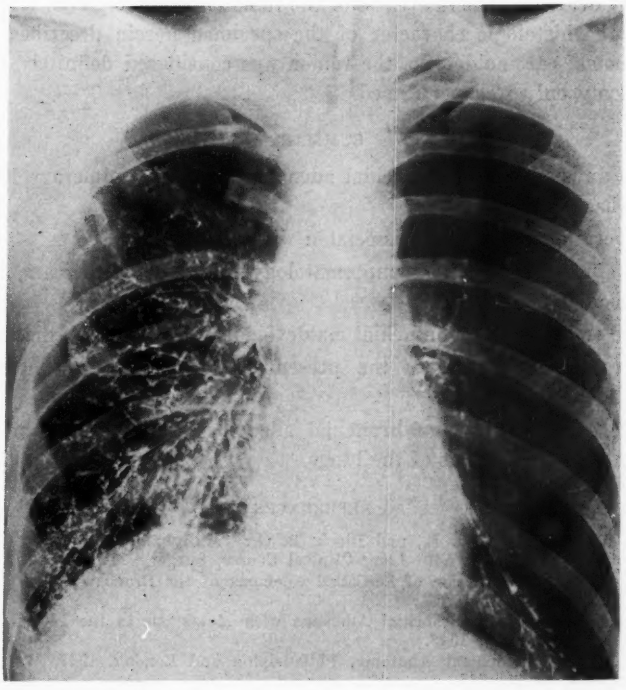

Fig. 6.—Lipiodol bronchogram which demonstrates the filling of all three lobes on the right side.

Embryologic maldevelopment has to be the probable explanation for this anomaly. Arey[4] has stated that some variations may occur in the size and the number of the major lobes of the lungs. For example, the eparterial bronchus in the human on the right side may originate directly from the trachea as in the sheep, pig, and ox; it may also imitate the relationship of the structures on the left side. Graham and Womack explain the etiology of many lung tumors as being due to failure of the embryonic bronchial buds to develop into normal structures. Although positive knowledge for the cause of developmental anomaly is lacking, there is reason to believe that in formation of the embryonic organs, most likely some intrauterine disturbance occurred.

Womack and Graham's[19] conception is that bronchial adenoma in which endodermal elements predominate are more malignant than others. It is true that the histopathology of so-called bronchial adenomas, as Graham has pointed out for many years, should be considered as potentially malignant tumors in spite of the fact that they usually remain benign for a long time. Authentic instances of metastases to the adjacent lymph nodes, vertebra, or liver have been reported by many authors.[1, 2, 3, 5, 9, 11, 19]

Since careful microscopic search through various parts of the tumor failed to show any evidence of invasiveness of the tumor into the regional lymph nodes, and since the histologic character of the specimen herein described was that of an adenoma, carcinoid type, the tumor was considered definitely as benign, and lobectomy only was performed.

SUMMARY

1. An unusual case of bronchial adenoma in a supernumerary lobe on the right side has been presented.

2. Several anomalies were associated with the tumor.

3. In spite of its severe symptomatology for almost ten years, the tumor remained benign.

4. The embryology of bronchial maldevelopment was briefly discussed.

5. Surgical extirpation is the present day accepted treatment for the bronchial adenoma.

6. The carcinoid type of bronchial adenomas is apparently more benign than the mixed type tumors of the lungs.

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A REVIEW OF SURGICALLY TREATED LUNG ABSCESS

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THIS study includes all cases of nontuberculous lung abscess receiving surgical treatment on the Chest Surgical Service at the Barnes Hospital in the six-year period 1943 through 1948. All lung abscesses, whether acute or chronic, putrid or nonputrid, were analyzed. A limited number of cases associated with partial bronchial stenosis were included, but in these instances the bronchial lesion apparently resulted from the parenchymal disease. All cases of saccular bronchiectasis with secondary focal abscess formation were eliminated. Abscesses resulting from bronchial obstruction by tumor or due to tumor necrosis were likewise excluded. No case of mycotic abscess or infected congenital cyst, where recognized as such, was considered.

In order to evaluate mortality rates and the changing trends in therapy, the six years covered by this review were divided into period I, representing the first three years, and period II, representing the second three years. The division roughly corresponds with the institution of antibiotic therapy in adequate dosage in conjunction with the surgical treatment of lung abscess.

One hundred five patients received surgical treatment for lung abscess during this six-year period. In Tables I and II additional untreated cases were included for the analysis of etiological factors and lobar distribution, making a total of 130 cases. Of these 130 cases, 76 were designated as of unknown etiology. Although in many instances the initial symptoms simulated those of acute pneumonia, we have not labeled these abscesses as postpneumonic in origin. Perhaps some of them were related to gingivodental infections. Of the 30 postoperative cases, 21 followed tonsillectomies. Dental extraction and aspiration of foreign body ranked next in importance with 7 and 5 cases, respectively.

TABLE I. ETIOLOGY

Unknown	76
Postoperative	30
Dental extraction	7
Aspiration foreign body	5
Septic infarct	4
Lateral sinus thrombosis	2
Chest trauma	2
Miscellaneous	4

TABLE II. LOCATION

RLL	35	(sup. seg.—16)
RUL	25	
LLL	20	(sup. seg.—5)
LUL	16	
RML	5	
Multilobar	29	
Lower lobes	55	
Upper lobes	41	
Right	65	
Left	36	

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Considering only those cases with monolobar distribution, the right lower lobe, the right upper lobe, the left lower lobe, and the left upper lobe were thus involved in order of frequency. This distribution corresponds to that reported by many authors. Of the 35 cases located in the right lower lobe, the superior segment was involved in 16. Further analysis of the monolobar cases reveals the lower lobes (55) to be affected somewhat more frequently than the upper lobes (41) and the right lung (65) considerably more frequently than the left (36). The predominance of the right lower lobe is taken as support for the aspiration theory of the formation of most putrid lung abscesses.

The over-all mortality rates for the surgically treated cases are presented in Table III. The mortality rates include patients dying of their disease following discharge from the hospital. The cases are separated into those having a drainage procedure as the initial treatment, either drainage of the abscess proper, or of an empyema secondary to the abscess; those having a primary resection; and those having a resection secondary to a drainage procedure. The 22 cases in the latter category include 11 cases having a drainage procedure performed before admission to Barnes Hospital. The over-all mortality rate of 30 per cent emphasizes the seriousness of this disease.

In Table IV, mortality figures are analyzed for periods I and II. A slight discrepancy appears in the figures, since secondary resections were performed during period II on three cases which were drained during period I. In each of the two categories a 40 to 60 per cent reduction in mortality was effected during period II. The mortality for drained (12 per cent) and resected (18 per cent) was approximately the same during period II. However, during period II, 20 primary resections for lung abscess were performed with only one death, a mortality of 5 per cent. The figures in Table IV not only reveal the improved mortality rates in both types of surgical treatment, i.e., drainage and resection, but also indicate an increasing application of resection therapy to this disease.

TABLE III. MORTALITY

	TOTAL	DEATHS	MORTALITY (PER CENT)
All surgically treated cases	105	31	30
Primarily drained	63	19	30
Primary resection	31	7	23
Secondary resection*	22	5	23

*11 cases previously drained at Barnes Hospital.
11 cases drained elsewhere.

TABLE IV. MORTALITY

		TOTAL	DEATHS	MORTALITY (PER CENT)
All cases	I	61	22	36
	II	55	9	16
Primarily drained	I	38	16	42
	II	25	3	12
All resections	I	20	6	30
	II	33	6	18

Table V relates the mortality of resection to the procedures of lobectomy and pneumonectomy. Not only was the mortality of pneumonectomy considerably higher, but it failed to show a significant improvement during period II. The higher mortality of pneumonectomy (47 per cent) as compared to lobectomy (13 per cent) may be attributed to the complexity and advanced state of the disease in patients requiring the former procedure and to the increased hazards of postoperative complications in patients from whom an entire lung has been removed.

The immediate causes of death are shown in Tables VI, VII, and VIII. During a drainage procedure, asphyxiation under anesthesia was caused in five cases by difficulty in handling secretions, blood, or vomitus. One case listed in this category might possibly be attributed to septic embolism. Four patients died of late hemorrhage from the abscess with infection playing a major role in most of these. Brain abscess will be mentioned subsequently.

Difficulty with secretions was a direct cause of death in at least one case among the primary resections, and was a contributory factor in at least one other case listed under shock. Secondary factors such as heart failure, pneumonitis, and wound infection played important roles in the three deaths listed as due to empyema and fistula. Among the secondary resections a variety of factors are listed as causes of death.

During the postoperative period following resection, the development of empyema and bronchopleural fistula contributed a considerable mortality and morbidity. Table IX illustrates the high incidence of this complication and the significant decrease during period II. The percentage of postresection empyemas dropped from 68 per cent in period I to 21 per cent in period II. The most important factors leading to this improvement were the intensive pre- and postoperative employment of antibiotic drugs and the assiduous application of the individual ligation technique. During period II tourniquet ligation was required only once. In the ten cases in which tourniquet ligation was employed, empyema and fistula developed in seven of these, and the other three died early before the formation of an empyema.

TABLE V. LOBECTOMY VERSUS PNEUMONECTOMY

	TOTAL	DEATHS	MORTALITY (PER CENT)
	Lobectomy		
Period I	14	3	21
Period II	24	2	8
Total	38	5	13
	Pneumonectomy		
Period I	6	3	50
Period II	9	4	44
Total	15	7	47

TABLE VI. CAUSES OF DEATH IN DRAINED CASES

6 Brain abscess
5 Asphyxiation under anesthesia
4 Hemorrhage (and infection)
2 Heart disease and pulmonary insufficiency
2 Debility and sepsis

TABLE VII. CAUSES OF DEATH IN PRIMARY RESECTIONS

3	Shock (? anoxia)
3	Empyema and fistula (other secondary factors)
1	Asphyxiation under anesthesia

TABLE VIII. CAUSES OF DEATH IN SECONDARY RESECTIONS

1	Shock
1	Empyema and fistula
1	Pulmonary insufficiency
1	Tension pneumothorax
1	? Abscess in contralateral lung

TABLE IX. POSTRESECTION EMPYEMA

	TOTAL CASES	WITH EMPYEMA	PER CENT
Primary resection	31	10	33
Secondary resection	22	10	45
Total	53	20	38
		Period I	68
		Period II	21

Our study revealed a decrease in the number of drainage procedures performed in two stages. In period I, 33 per cent of the drainage procedures were carried out in two or more stages, whereas during period II only 13 per cent required two stages. This trend probably signifies not only a more accurate localization of abscesses with roentgenographic examination, but a tendency to employ resection therapy for the more complicated and inaccessible abscesses. Neuhof[1] has pointed out that very few putrid lung abscesses require a two-stage drainage procedure except possibly in the case of those located near interlobar fissures, the diaphragm, and the mediastinum.

Table X indicates that 25 per cent of cases treated by drainage subsequently required a secondary revision. A total of 27 revisions were performed on 18 patients. Revisions were necessary for a variety of reasons: inadequate drainage, premature closure of the sinus tract, recurrence of abscess, or for drainage of additional abscesses.

Empyema secondary to lung abscess and occurring prior to surgical therapy was encountered in thirteen patients. In eight of these it was possible to drain the empyema and abscess simultaneously; in five separate or additional drainage procedures were required.

In this series, drainage of lung abscess has been associated with a significant number of nonfatal as well as fatal complications. In Table VI are listed the causes of death in the drained cases. In addition to the four fatal hemorrhages there were three other serious but nonfatal hemorrhages. Empyema followed pneumonotomy in nine cases, but in only one of these did it appear to be a contributing cause of death. In three instances wound infection occurred between the first and second stages of drainage procedures. In three instances patients returned with an aspiration spread, in two of the cases to the contralateral lung. In three cases metastatic spread of infection to other regions of the body other than the brain occurred.

TABLE X. REVISION AFTER DRAINAGE PROCEDURE

	NO. OF CASES
1. After pneumonotomy	
one revision	9
two revisions	5
three revisions	1
2. After empyema drainage	
one revision	1
two revisions	2

Brain abscess developed in seven patients who were surgically drained, in no patients in whom resection was employed. Six of the seven patients died of this complication; one patient was cured by excision of brain abscess. In two of four patients examined postmortem, undrained lung abscesses were found.

LATE RESULTS

An evaluation of the status of the patients at least one year following the latest case has been attempted. Our estimates of the final results were based on individual examinations or questionnaires. The questionnaire included inquiry regarding cough, sputum, hemoptysis, pain, and physical activity. A significant proportion of patients could not be contacted.

Of the 105 patients treated, 41, or 39 per cent, were considered cured; 31, or 30 per cent, were dead from their disease; 13, or 12 per cent, were living but not cured; and 20, or 19 per cent, could not be traced.

Patients treated by drainage:

63 cases—19 deaths (from complications of lung abscess or from operation)
44 survivals
11 secondary resections
2 deaths
4 cured
2 improved
3 not traced
33 others
6 not traced
1 died from other disease
26 followed

Of the 26 patients followed, 20 could be considered cured and six improved. Of the six improved patients, three still had some drainage from the wound, six continued to raise sputum, five had coughed up blood since discharge, and six had varying degrees of chest pain. Thus only 32 per cent of the original 63 patients were known to be cured without resort to secondary resection. With complete follow-up it was statistically possible for 41 per cent to have obtained a cure.

Patients treated by primary resection:

31 cases—7 deaths
24 survivals
8 not traced
16 followed

Of the 16 patients followed, 13 could be considered cured, one improved, and two unimproved. Of the three patients not cured, three were still having some drainage from the wound, three continued to raise sputum, two had coughed up blood since discharge, and two had varying degrees of chest pain. Thus of the original 31 patients, 42 per cent were known to be cured. With complete follow-up, it was statistically possible for 68 per cent to have obtained a cure.

Patients treated by secondary resection (includes 11 patients previously drained at Barnes Hospital and 11 patients drained elsewhere):

22 cases—5 deaths
17 survivals
5 not traced
12 followed

Of the 12 patients followed, eight could be considered cured and four improved. Of the four patients not cured, none were having drainage from their wounds, four continued to raise sputum, four had coughed up blood since discharge, and three had varying degrees of chest pain. Thus only 36 per cent of the original 22 patients were known to be cured. With complete follow-up, it was possible for 59 per cent to have obtained a cure.

DISCUSSION

Valle[2] previously reviewed the cases of lung abscess seen on the Chest Surgical Service at Barnes Hospital between 1932 and 1943. One hundred sixty-four patients with lung abscess were treated surgically, with a mortality rate of 38.8 per cent. Twenty-eight lobectomies and two pneumonectomies were included in that series, but a breakdown of the mortality rate into drained and resected cases was not presented. The reduction in mortality to 30 per cent during the six-year period 1943 through 1948, and to 16 per cent from 1946 through 1948 is gratifying, but even these more recent figures emphasize the serious nature of the disease. Our series includes a high percentage of multiple and multilobar abscesses which would suggest a high proportion of neglected cases with complicated disease.

Comparison with other reported series is of interest. Sweet[3] analyzed the cases of lung abscess seen at the Massachusetts General Hospital between 1940 to 1945. Seventy-five patients were subjected to operation, with a mortality of 15 per cent. A cure rate of only 31 per cent was obtained in the drained patients without resort to secondary resection. Fifteen primary lobectomies and eleven secondary resections were performed with two deaths. No pneumonectomies were included in his series. The series reported by Neuhof[1] is hardly comparable since it contains only cases of putrid lung abscess drained within six weeks of the onset of the disease. However, he obtained the extremely low mortality rate of 2.3 per cent using drainage as the only method of surgical attack. In this same series he indicated a very high cure rate.

Recently several authors have reported very favorable results with the frequent use of pulmonary resection. Shaw and Paulson[4] reported 52 resections

performed for chronic putrid lung abscess with two deaths, a mortality of 3.8 per cent. The postoperative empyema rate, however, reached 28.8 per cent. Kent and Ashburn[5] reported 30 cases of chronic lung abscess treated similarly with two deaths, a mortality of 6.6 per cent, with an empyema rate of 6.6.

The trend on the Chest Surgical Service at Barnes Hospital in the past few years has led to the more frequent use of lobectomy and pneumonectomy. Segmental resection has been employed only rarely. As specific indications for the employment of primary resection in the treatment of lung abscess, the following may be listed: (1) multiple lung abscesses; (2) associated bronchial stenosis; (3) extended chronicity with fibrosis and secondary bronchiectasis; (4) suspicion of bronchial adenoma or carcinoma; (5) suspicion of infected congenital lung cyst; (6) abscess somewhat inaccessible to drainage; (7) simple lung abscess in the good risk patient which is failing to respond to conservative treatment.

SUMMARY

1. As a result of improved surgical techniques and extensive use of antibiotics, the mortality of surgically treated lung abscess at the Barnes Hospital has declined from a previously reported rate of 38.8 per cent prior to 1943 to 16 per cent from 1946 through 1948.

2. The frequent employment of pulmonary resection in many instances in preference to drainage has contributed significantly to reduction in mortality as well as improvement in the cure rate, particularly in the complicated cases.

3. The postresection empyema rate decreased from 68 per cent from 1943 through 1945 to 21 per cent from 1946 through 1948. This reduction coincided with intensive use of antibiotics as well as the more general application of individual ligation technique.

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BRONCHOSCOPY IN THE TREATMENT OF SPONTANEOUS AND TRAUMATIC PNEUMOTHORAX

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THE treatment of spontaneous or uncomplicated traumatic pneumothorax, as a rule, presents few difficulties. The air in the pleural cavity is absorbed in a few weeks; at most, one or more aspirations are necessary to hasten re-expansion of the lung. In the presence of tension pneumothorax associated with intrathoracic pressure symptoms, continuous air deflation is instituted by means of water-sealed drainage with or without negative suction. The instillation of irritating substances into the pleural cavity in an attempt to induce a sterile pleurisy and thereby obliterate the pneumothorax is another method of treatment. Silver nitrate, hypertonic glucose solution, gomenol, or the patient's own blood is used for the purpose. But inasmuch as the induction of so-called provocative or chemical pleuritides is not always effective nor devoid of danger of causing an intense pleural reaction with possible permanent impairment of lung function, this method of treatment is losing favor. Instead, an increasing number of patients with chronic or recurrent pneumothorax are being submitted to operation with the aim of resecting the ruptured bleb or cyst, or even the entire lobe if the latter is a source of repeated blowouts. Direct surgical treatmet is also displacing intrapleural pneumonolysis which is used occasionally to free the lung of suspending adhesions permitting closure of the pleural opening. The forementioned are, in brief, the current methods of treating nontuberculous pneumothorax.

Except for passing reference to the use of bronchoscopy for diagnostic purposes, a review of the literature on spontaneous and traumatic pneumothorax does not reveal a single report which stresses the need of this measure as an integral part of the treatment in certain cases. This is surprising in view of the fact that a lung collapsed by pneumothorax may fail to reinflate not because of factors relating to the lung rupture or to the pneumothorax, but as a result of bronchial obstruction. Viscid secretion, clotted blood, or other types of impaction within bronchi or bronchioli may prevent the ingress of air into the lung, thus maintaining the organ in a state of collapse. This has been our experience in two patients with spontaneous pneumothorax and two with traumatic pneumothorax. In each instance bronchoscopy, when other measures failed, was used with gratifying results.

REPORT OF CASES

CASE 1.—T. K., a student, aged 17 years, developed an upper respiratory infection. That same night he was seized with severe chest pain, fever, cough, and dyspnea. He was admitted to a hospital where he was given penicillin for suspected pneumonia. A roentgeno-

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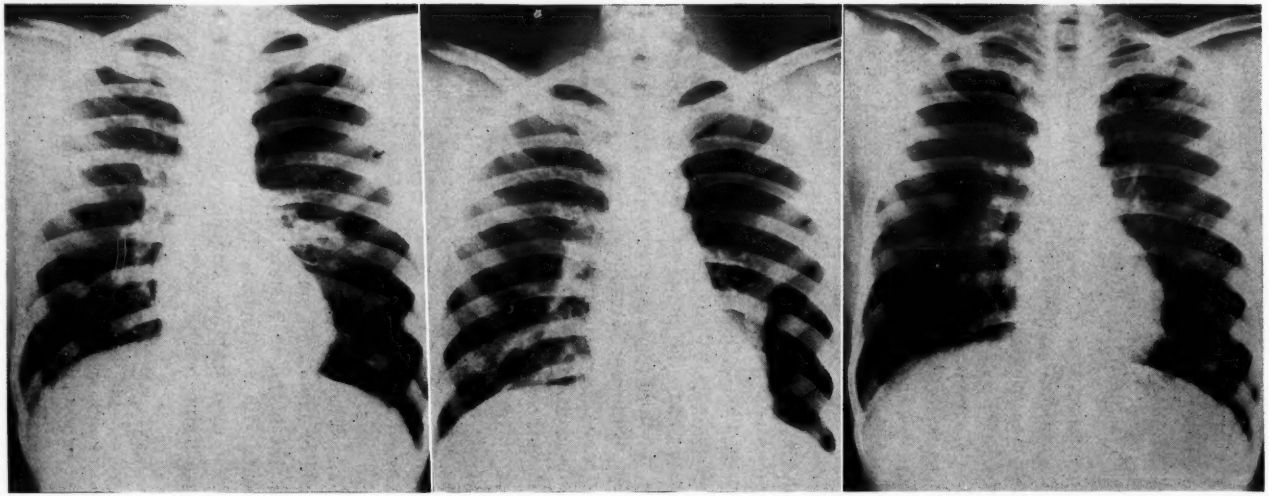


A. *B.* *C.*

Fig. 1.—(Case 1, T. K.) Roentgenograms of a boy of 17 years showing atelectasis in the presence of a spontaneous pneumothorax. Before and after bronchoscopic aspiration. *A*, Feb. 24, 1950. Pneumothorax on left collapsing about 50 per cent of lung; no adhesions or fluid; heart not displaced. *B*, Feb. 28, 1950. Increase in size of pneumothorax the left lower lobe being almost completely collapsed; small amount of fluid at left base; heart slightly displaced to left. (Bronchoscopy, March 7, 1950.) *C*, March 20, 1950. Pneumothorax completely absorbed; no gross abnormalities seen.

A. *B.* *C.*

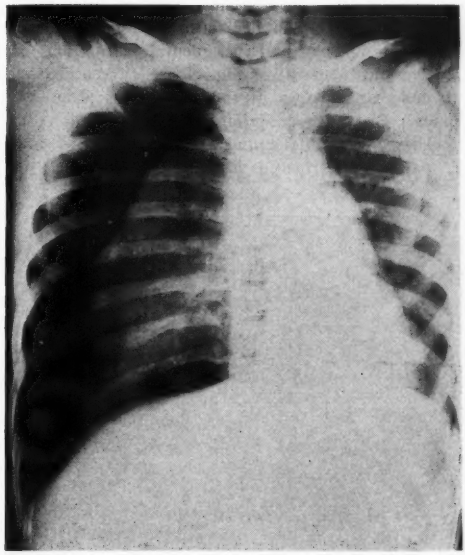
Fig. 2.—(Case 2, T. S.) Roentgenograms of a woman of 20 years showing atelectasis and massive effusion in the presence of a spontaneous pneumothorax. Before and after bronchoscopic aspiration. *A*, March 8, 1949. Pneumothorax on left collapsing about a third of the lung; no adhesions or fluid; heart slightly displaced to right. *B*, March 12, 1949. Left lung is almost completely collapsed by a massive hydropneumothorax. (Bronchoscopy, March 12, 1949.) *C*, April 30, 1949. Left lung has reexpanded; a small collection of air is still seen at extreme apex.

gram of the chest the following day revealed a left-sided pneumothorax, the lung being collapsed to about 50 per cent of its volume. The heatrt was not displaced; no fluid or adhesions (Fig. 1*A*). Aspiration of air from the chest was followed by slight relief. Four days later, a roentgenogram revealed a decided increase in the degree of pulmonary collapse, especially of the left lower lobe. A small effusion was present at the base (Fig. 1*B*). The patient's dyspnea, cough, and fever became aggravated. Repeated aspirations of air did not reduce the size of the pneumothorax. At this time the patient was seen by us. It was suspected that he had a bronchial obstruction due to impacted sputum incident to his antecedent respiratory infection, and that this was the cause of the complicating atelectasis of the left lower lobe. Bronchoscopic aspiration was followed immediately by partial aeration of the lung with coincident improvement in the patient's symptoms. By the end of a week, and without the need of additional air removal, the lung reexpanded about 50 per cent and in three weeks, completely. Neither lung revealed parenchymal disease (Fig. 1*C*).

CASE 2.—T. S., housewife, aged 20 years, became suddenly ill with severe pain in the left chest, shoulder, and arm. After twenty-four hours, she developed increasing shortness of breath so that by the time she consulted us she was in acute respiratory distress. A roentgenogram of the chest taken the day after the seizure showed a pneumothorax collapsing about a third of the left lung. There was no fluid in the pleural space, no adhesions, and only slight displacement of the heart to the right (Fig. 2*A*). However, a film taken at the time she came to our office four days after the seizure revealed almost complete collapse of the left lung with fluid occupying half of the pleural cavity (Fig. 2*B*). During the following two days, three aspirations were made of serous fluid (totalling 1,000 c.c.) and an indeterminate amount of air. The intrapleural pressure which was initially slightly positive became negative. Because of the persistent cough and expectoration of thick green sputum, which the patient had had from the onset of the illness, as well as the sudden marked change in the appearance of the roentgenogram, it was suspected that bronchial obstruction was a complicating factor. Bronchoscopy revealed the right main bronchus and all its subdivisions normal and free of secretions. The left main bronchus appeared narrowed; the branch to the lower lobe contained thick green secretion which was aspirated. The following day the patient felt greatly relieved. A roentgenogram taken two days later showed considerable reaeration of the left lung. In six weeks, and without additional aspirations, the pneumothorax was absorbed, except for a small residue of air at the extreme apex (Fig. 2*C*). A subsequent film showed the lung completely reexpanded.

CASE 3.—N. M., a girl, aged 8 years, was brought by ambulance to the Morrisania City Hospital after having been struck by an automobile. The child was in critical condition, unconscious, cyanotic, and dyspneic. She was placed in oxygen, an infusion of 500 c.c. of plasma started, given penicillin and other supportive measures. A roentgenogram of the chest taken the day of the accident revealed a partial collapse of the right lung by a pneumothorax with displacement of the mediastinum and heart into the left chest. A fracture was noted of the right eighth rib posteriorly (Fig. 3*A*). A roentgenogram the following day showed a marked increase in the degree of collapse of the lung, especially of the right upper lobe; fluid was present at the base (Fig. 3*B*). It was suspected that a superimposed atelectasis had occurred as a result of bronchial obstruction. Two chest aspirations yielded about 200 c.c. of air and 180 c.c. of serosanguineous fluid, but the lung failed to reexpand. Bronchoscopy was done the following day and viscid sputum aspirated. The patient's condition took an immediate turn for the better. The air in the chest was quickly absorbed, without the need of further aspirations, and by the time of discharge, two weeks later, the lung had reexpanded completely (Fig. 3*C*).

CASE 4.—V. K., a man, aged 22 years, was admitted to the Morrisania City Hospital three and one-half hours after having been stabbed twice in the right axilla. The patient's only complaint was pain on deep breathing. Examination of the chest showed a closed stab wound in the right lower chest. The breath sounds were diminished to absent on that side. A roentgenogram taken the same day revealed a right-sided pneumothorax with the lung



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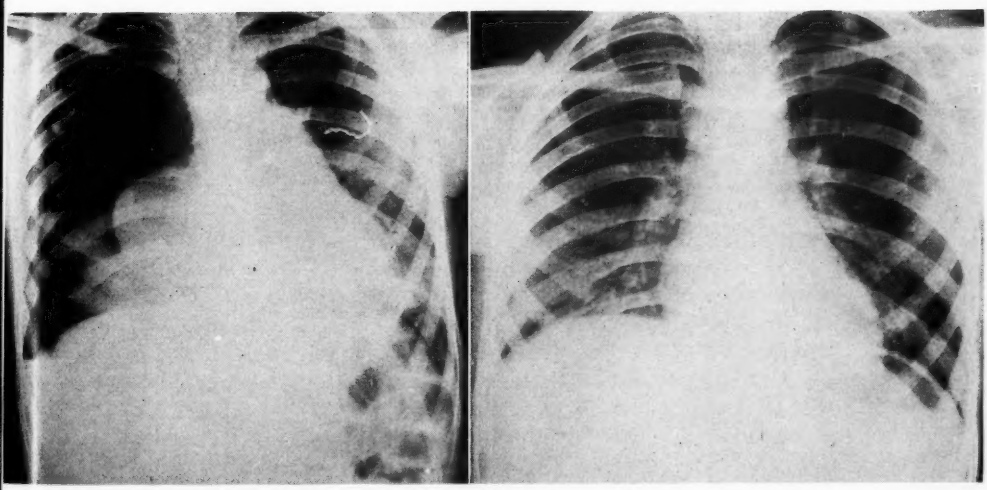
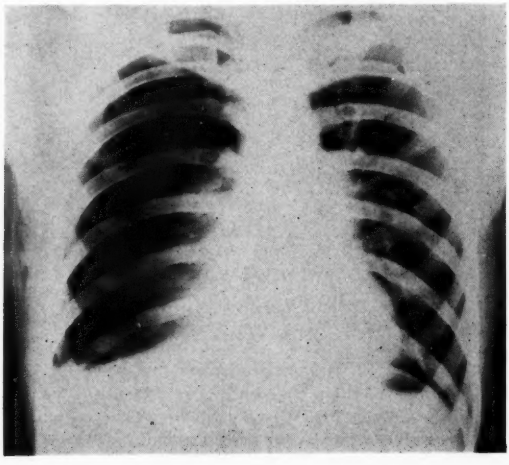


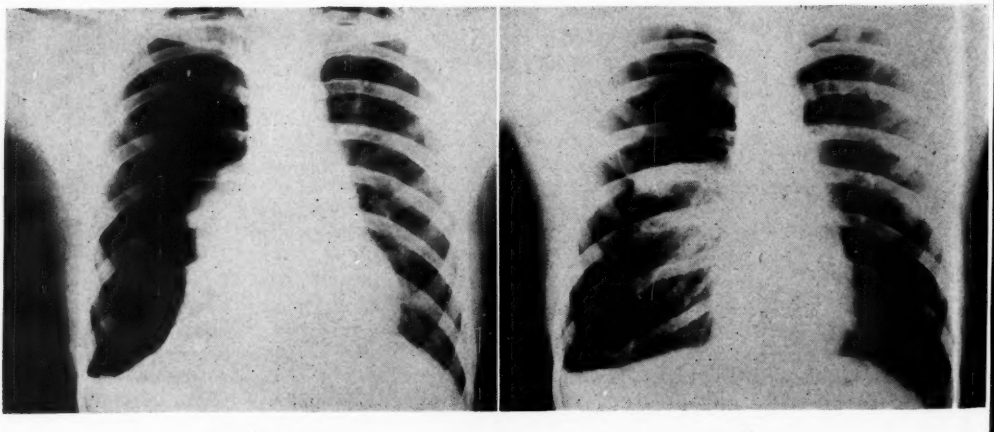
B. *C.*

Fig. 3.—(Case 3, N. M.) Roentgenograms of a girl of 8 years showing atelectasis in the presence of a traumatic pneumothorax. Before and after bronchoscopic aspiration. *A*, June 8, 1949. Pneumothorax on right collapsing about half of lung; no adhesions or fluid; considerable displacement of heart and mediastinum to left; fracture of eighth rib on right. *B*, June 9, 1949. Marked increase in degree of collapse of right lung, especially of upper lobe; small amount of fluid at right base (Bronchoscopy, June 10, 1949). *C*, June 24, 1949. Right lung completely reexpanded; no gross abnormalities seen.

collapsed about 50 per cent of its volume. There were no adhesions; a small effusion obliterated the right costophrenic sinus. The mediastinal contents were not displaced (Fig. 4*A*). The treatment consisted of air removal and intrapleural instillations of penicillin and streptomycin. Eleven days later, a comparative film showed a marked increase in the size of the pneumothorax with complete collapse of the right lung (Fig. 4*B*). At this time, the patient developed dyspnea. On the assumption that the right lung had sustained a superimposed atelectasis, bronchoscopy was done, and a large amount of mucus aspirated. Following bronchoscopy, the patient experienced immediate relief and no longer required air



A.



B. *C.*

Fig. 4.—(Case 4, V. K.) Roentgenograms of a man of 22 years showing atelectasis in the presence of a traumatic pneumothorax. Before and after bronchoscopic aspiration. *A*, June 22, 1950. Pneumothorax on right collapsing about 50 per cent of lung; no adhesions; small amount of fluid at right base. Subcutaneous emphysema in right axillary region. *B*, July 3, 1950. Marked increase in size of pneumothorax, the right lung almost completely collapsed. (Bronchoscopy, July 7, 1950.) *C*, July 10, 1950. There is considerable reexpansion of right lung; a patch of atelectasis still present in right upper lobe; small effusion persists.

aspirations. A film taken three days later showed considerable reaeration of the lung, a patch of atelectasis still being present in the right upper lobe (Fig. 4*C*). The patient left the hospital before the lung had reexpanded completely.

Our initial experience with bronchoscopic suction in the treatment of a nonexpanding lung was in a dentist, aged 37 years, who developed a spontaneous pneumothorax immediately following an injection of histamine which he had been receiving for the relief of migraine. The patient was taken to a hospital where a pneumothorax was found collapsing about 75 per cent of the right lung. After several days, he returned home, comfortable but somewhat dyspneic. Three weeks later, shortly before consulting us, he had a recurrence of chest pain and the dyspnea became severe. Examination at this time revealed a right-sided pneumothorax with almost complete collapse of the lung. For several days the patient was treated by daily withdrawals of 500 to 1,000 c.c. of air. It was noted that after the removal of air the pressure, which was initially positive, became negative, but as soon as the patient began to cough and exert himself the pressure became again positive. This, and the fact that several of the films revealed a circumscribed translucency overlying the right upper lobe, suggested that a ruptured bleb was the underlying cause. In the belief that bronchial obstruction, incident to a probable bronchospasm following the injection of histamine, might be preventing reaeration of the lung, bronchoscopy was done. The right main bronchus was found occluded by a plug of gray mucus which was aspirated. The bronchi were visualized and no pathologic changes noted. In spite of bronchoscopic suction and strenuous attempts to reexpand the lung, there was little change in the patient's condition. Bronchoscopy was repeated and, at this time, an effort was made to aspirate the small bronchi by means of a narrow rubber catheter attached to the end of a metal aspirating tube. Additional measures consisted of under-water drainage and, on several occasions, the instillation of the patient's own blood into the pleura in the hope of provoking a pleural reaction. These measures were also of no avail. One day following an intrapleural injection of 100,000 units of penicillin, which the patient had received twice previously, he developed a generalized erythematous eruption of the skin associated with itching and a rise in temperature. Coincidentally, a small effusion appeared in the pneumothorax space. Shortly thereafter the pneumothorax began to be obliterated, and in two weeks the lung reexpanded completely. Although not comparable with the first four cases cited, because of complicating factors, the indication in this case for attempting to open up bronchial channels seemed clear cut. Currently, the demonstration of a bleb or cyst in a patient with chronic or recurrent pneumothorax would be an indication for exploratory thoracotomy.

DISCUSSION

In each of the first four cases cited, a partially deflated lung, in the presence of a pneumothorax, sustained additional collapse as a result of superimposed atelectasis. The occurrence of the latter was suspected from a sudden change in the appearance of comparative roentgenograms which revealed an increase not only in the extent of the collapse but also in the degree of airlessness of the affected lung. A pleural effusion often appeared coincidentally. The symptoms were in keeping, the cough, expectoration, dyspnea, and fever becoming more pronounced. Furthermore, in each case there was an antecedent history either of respiratory infection or chest trauma, predisposing factors in the development of bronchial obstruction. Inasmuch as the condition was rapidly resolved following bronchoscopy without additional air withdrawals, it would seem to confirm the diagnosis and the rationale of the treatment.

Even if bronchoscopy does not reveal obstruction, it does not necessarily exclude its presence beyond bronchoscopic view. If there is demonstrable pulmonary atelectasis, or if there is an antecedent history to make one suspect

bronchial obstruction, an attempt should be made to cleanse the bronchi of secretion in any event. It is well to bear in mind that in the presence of negative intrathoracic pressure, which exists in a low-tension pneumothorax, the inspiratory pull preceding cough and exertional dyspnea serves to draw mucus from larger into smaller bronchi, and as the latter become plugged there is progressive atelectasis of distal segments of the lung. The main bronchi in such cases may not be visibly obstructed.

CONCLUSION

Bronchial obstruction with or without demonstrable atelectasis may complicate a spontaneous or traumatic pneumothorax preventing reaeration of the lung in spite of strenuous attempts to obliterate the pneumothorax space. It is essential, therefore, that in obstinate cases bronchoscopic aspiration be employed to cleanse the bronchi of secretion and allow ingress of air in addition to attempts at obliterating the pneumothorax space by conventional methods of treatment.

THE PULMONARY ARTERY IN BRONCHIECTASIS

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MUCH has been written about bronchiectasis as a disease entity, and more recently numerous investigators have called attention to the presence of bronchiectasis complicating pulmonary tuberculosis. Dormer and his associates[1-5] in South Africa, who have done bronchograms on more than 2,000 patients with tuberculosis, have suggested that the complication of bronchiectasis is very common and often is of such clinical moment as to overshadow the tuberculosis and render collapse ineffective. Norris and Landis[6] stated that bronchiectasis is present in more than 21 per cent of tuberculous lungs seen at autopsy. Jones[7] and her co-workers recently have reported on the relationship between tuberculosis and bronchiectasis, but made no mention of the possible functional differences between the disease entity bronchiectasis and bronchial ectasia encountered in tuberculosis. Liebow and associates[8] have drawn attention to the role of the bronchial arteries in this disease. The term bronchiectasis as used in this paper denotes the pulmonary disorder characterized by dilatation of the bronchi and pathologic changes in the bronchial wall and adjoining tissues which are found as a sequel to many varied and apparently unrelated conditions which include bronchopneumonia, lung abscess, neoplasm, and influenza. It does not include bronchial ectasia commonly associated with pulmonary tuberculosis. Although the study of the pulmonary arteries by injection of a contrast media is not new, little has been written about the pulmonary arteries in bronchiectasis and their possible role in altered function. The following studies were limited to the bronchial tree and to the pulmonary arteries, for they are readily accessible, and any alteration in either of these two should be reflected in an alteration in function.

MATERIALS AND METHODS

While numerous materials were used as contrast media, iodized oil was found to be most suitable. As soon as each lung specimen was obtained from either the operating room or the autopsy table, the pulmonary arteries were cannulated and the iodized oil injected under fluoroscopic observation. The cannulae were then removed, the vessels ligated to prevent retrograde spilling of the iodized oil, and roentgenograms taken. The bronchi then were injected in a similar manner with care being taken to avoid overfilling so as to prevent

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passage of the oil into the alveoli. Roentgenograms were again taken. Using this method, lungs were studied which had the classical lesions of primary bronchiectasis and tuberculosis. Normal lungs were also studied.

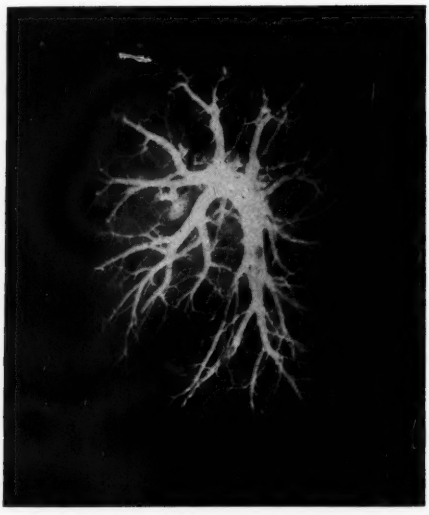

Fig. 1.—Normal lung in which the pulmonary artery has been injected with iodized oil. Note the gradual tapering and increased branching of the vessels which form a delicate and uniform pattern throughout the lung.

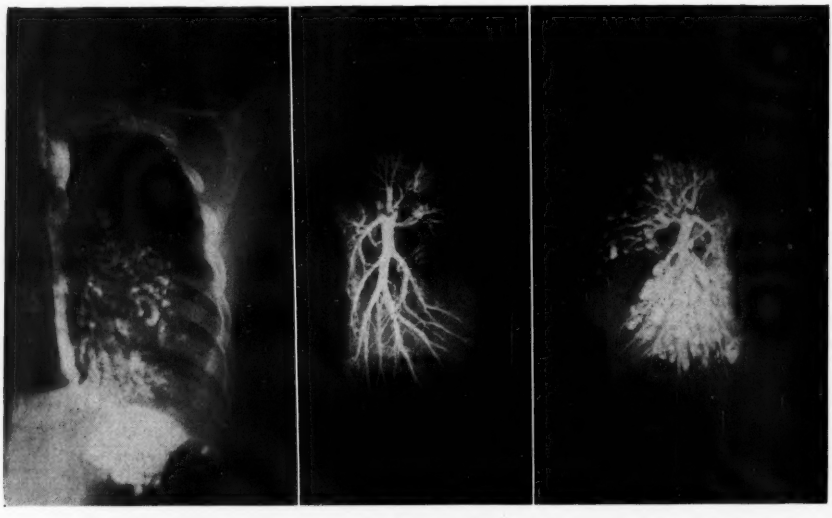

Fig. 2.—*Left.* Bronchogram of a patient with extensive bronchiectasis of the left lung. The radiolucent area in the left upper lung field represents an area of lung hernia from the right. *Middle.* Excised left lung from same patient with the pulmonary artery injected with iodized oil. Note the similarity of the pulmonary arterial pattern with that of Fig. 1. *Right.* Same lung with bronchi injected with iodized oil illustrating the extreme degree of bronchiectasis. The dense area at the periphery of the lower lobe which is not penetrated by either pulmonary artery or bronchi is due to a subpleural hematoma which developed at the time of resection.

RESULTS

The pulmonary artery in the normal lungs showed the major branches giving rise to smaller radicles which diminished in caliber as they approached the periphery of the lung. The gradual tapering and increased branching of the vessels formed a delicate and uniform pattern throughout the lung down to vessels of precapillary size. In no place were they widened, shortened, or distorted (Fig. 1).

The pattern of the pulmonary artery in bronchiectasis of the nontuberculous lung was the same as that seen in the uninvolved lungs (Fig. 2). The major branches were uniform in size and gave rise to small radicles which had a similar delicate arborization as observed in the normal lung.

Fig. 3.—*Left.* Posterior-anterior roentgenogram of the chest taken shortly before death. This patient had fibrocaseous pulmonary tuberculosis of the entire left lung. Following thoracoplasty on the left there was spread of disease to the right lung with production of fibrocaseous disease and cavitation throughout the upper half of the lung field. *Right.* Specimen from the same case from which the heart and both lungs were removed en bloc. Note the complete absence of branches of the pulmonary artery throughout the periphery of the left lung, right upper lobe and superior segment of the right lower lobe. In the right lower lobe which is relatively free of disease there is a normal pulmonary arterial pattern.

On the contrary, in tuberculosis the pulmonary arterial pattern was markedly altered in the areas of fibrocaseous disease (Fig. 3). Many of the larger branches were shortened, narrowed, and irregularly distributed. There was a marked paucity of the smaller branches in areas of fibrotic disease, and complete absence in areas of caseation. This same pulmonary arterial pattern was present whether bronchial ectasia was present or absent in these tuberculous areas.

DISCUSSION

In a consideration of functional capacity of the lung, the presence of pathologic changes becomes important. Fibrocaseous tuberculosis is accompanied invariably by an obliterative arteritis. Thus, the areas of the lung which are poorly ventilated due to a tuberculous process are in turn poorly circulated, and one would not expect unsaturated blood returned to the left auricle from

these areas. This is borne out in respiratory physiologic studies in tuberculous patients; namely, arterial oxygen unsaturation usually is not found at rest. Carvalho[9] recently found that angiocardiopneumographic examinations performed on living tuberculous patients showed the pulmonary circulation in the areas of disease to be either absent or deficient. He also states that, contrary to the above, angiocardiopneumographic examinations show increased blood

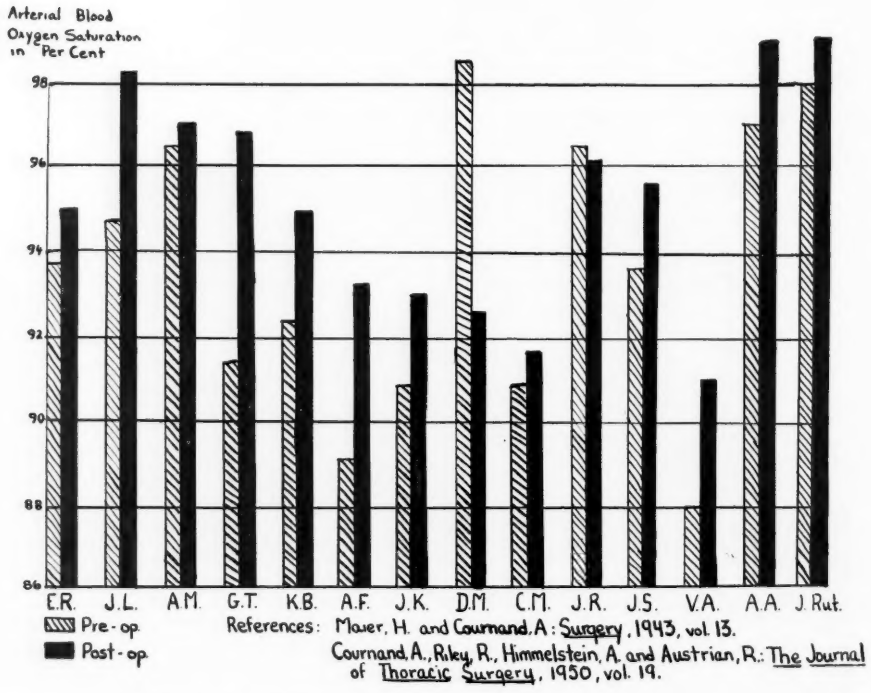

Fig. 4.—Table compiled from published papers of Maier, H., Cournand, A., Riley, R., Himmelstein, A., and Austrian, R. The first column in each group of two denotes the preoperative arterial blood oxygen saturation in per cent. The second column in each group denotes the postoperative level. There is a consistent elevation in the postoperative levels except in one case, J. R., which shows practically no change and in D. M., who shows a marked decrease in the postoperative level. For discussion see text.

supply at the region of lung abscesses. He concludes that he is thereby able to distinguish between the images of tuberculosis and those of common inflammatory nature. Steinberg[10] verified by angiocardiopneumography the avascularity of tuberculous parenchymal lesions reported by Carvalho.

Lisa and Rosenblatt,[11] in their histologic study of 110 cases of bronchiectasis, found that the blood vessels in the vicinity of the affected bronchi showed no general changes except in one case which showed a productive endarteritis. If there is blood flow through the intact pulmonary arteries that have been demonstrated above in areas of nontuberculous bronchiectasis, then there is circulation without ventilation, and one should expect decreased systemic arterial

oxygen saturation. Although the blood flow through the pulmonary arteries in areas of primary bronchiectasis has not been studied, the arteries are intact for perfusion. Such an arrangement as is here demonstrated suggests a shunt mechanism in that venous blood flows through the unventilated diseased portion of the lung and returns to the left auricle as venous blood where it mixes with blood from other areas of the lung that are normally circulated and ventilated. Maier and Cournand,[12] and Cournand, Riley, Himmelstein, and Austrian[13] studied pre- and postoperative arterial oxygen saturations on a number of bronchiectatic patients who underwent pulmonary resections. They found definite improvement in the postoperative arterial oxygen saturation in twelve of fourteen cases, one patient showing no difference (Fig. 4). The patient who showed considerable decrease in his postoperative arterial oxygen saturation had the complication of postoperative left upper lobe atelectasis. Maier and Cournand,[12] in speaking of the postoperative complications of atelectasis, state that: "Since a considerable amount of blood may be flowing through the pulmonary vessels of a poorly ventilated lobe, arterial oxygen unsaturation results."

SUMMARY

Injections of the pulmonary arteries with a radio-opaque material in cases of nontuberculous bronchiectasis reveal a normal pattern in contrast to tuberculosis, and suggest that the arteries are intact for perfusion. Following resection of the bronchiectatic portion of the lung, there is an increase in the arterial oxygen saturation. This improvement is thought to be due to the removal of the poorly ventilated but adequately circulated diseased portion of the lung which is acting as a venous-arterial shunt mechanism. Respiratory physiologic studies support this observation.

In fibrocaseous pulmonary tuberculosis there is an irregularity of the large branches and a marked paucity of the small branches in fibrotic areas and complete absence in areas of caseation. The absence of circulation in the poorly ventilated areas is an explanation for the findings of normal arterial oxygen saturation in pulmonary tuberculosis at rest despite loss of considerable pulmonary tissue.

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LIVER HERNIATION SIMULATING INTRATHORACIC TUMOR

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HERNIATION of all or part of the right lobe of the liver through the diaphragm is uncommon, having been described in only six instances.[1-6] In 857 cases of diaphragmatic hernia reviewed by Hedblom,[7] protrusion of the liver into the chest occurred in only fourteen patients. Since the presence of liver tissue in the chest may closely simulate a mediastinal or pulmonary tumor, the correct diagnosis is usually not made (or entertained) prior to operation or autopsy. In order to direct attention to hepatic herniation as a possibility to be considered in the differential diagnosis of rounded shadows in the right lower lung field which are contiguous with the diaphragm, an illustrative case is cited.

CASE REPORT

A 63-year-old German sheet metal worker (N.Y.H. 507 327) was admitted complaining of epigastric pain of twelve years' duration and a twenty-five pound weight loss during the preceding year. Forty-four years ago, at the age of 19 years, he had fallen seventy-five feet, sustaining a cerebral concussion and multiple fractures; no history of abdominal distress could be obtained. Twelve years ago he first noted sharp, localized epigastric pain usually occurring about two hours after meals and relieved by belching. The pain gradually changed to a constant, dull, epigastric aching with occasional episodes of sharp, knifelike pain lasting a few minutes. There was no history of nausea, vomiting, hematemesis, jaundice, diarrhea, anorexia, bloody or tarry stools. Only a slight cough had been noted. Physical examination was essentially normal.

Roentgenogram of the chest (Fig. 1) showed a large, homogeneous, sharply circumscribed mass in the right anterior chest. This did not pulsate on fluoroscopy, nor was there any evidence of a fluid level or areas of calcification. It could not be separated from the diaphragm. On the basis of the roentgenogram appearance, the mass was thought to be a pulmonary or mediastinal tumor. Pertinent laboratory examinations were unrevealing, and exploratory operation was decided upon.

At operation a large, round herniation of part of the right lobe of the liver was encountered, passing through the central portion of the dome of the diaphragm. The herniated portion was connected to the remainder of the liver by an 8-centimeter pedicle circumscribed by a tenuous band. The entire mass was removed by transecting its base, and the resulting defect in the diaphragm closed. The patient's postoperative course was uneventful with relief of symptoms. He died one year later due to a pneumococcus meningitis.

SUMMARY

This case is unique in that the traumatic diaphragmatic hernia probably had its onset forty-four years ago. Pain referable to the lesion came on thirty-two years later and may have coincided with incarceration of the herniated

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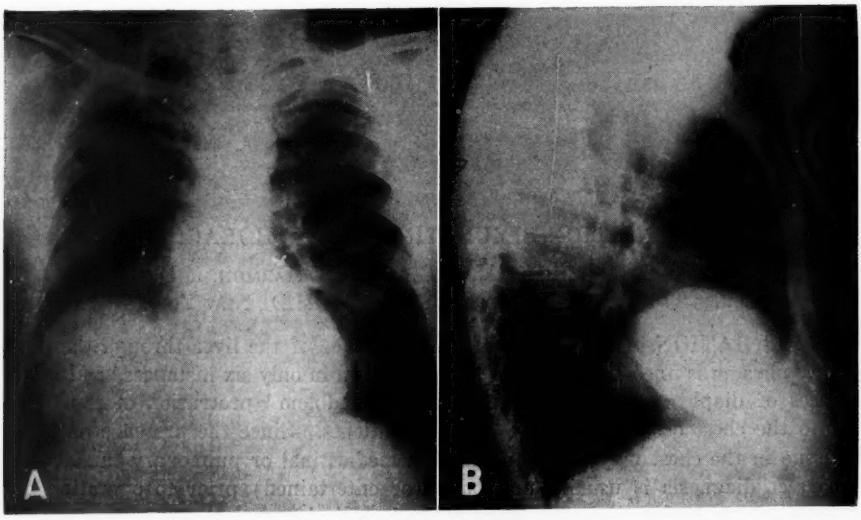

Fig. 1.—Liver Hernia. *A*, Frontal roentgenogram shows a large, rounded mass adjacent to the right heart border and contiguous with the diaphragm. *B*, Right lateral roentgenogram shows the anterior position of the mass which simulates an intrathoracic tumor.

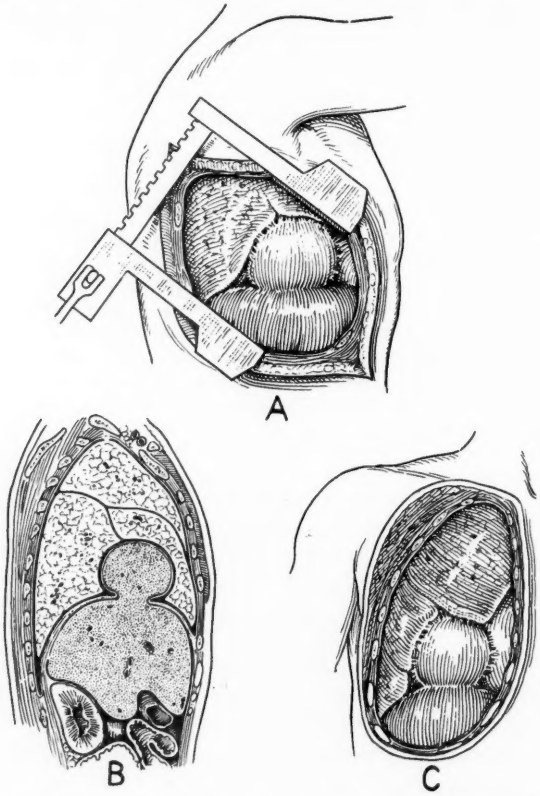

Fig. 2.—Liver Hernia, Operative Findings. *A*, Incarcerated portion of right lobe of liver protruding through central dome of diaphragm. *B*, Diagrammatic illustration of anatomic relations of liver, viewed in sagittal section through the hernia. *C*, Diagrammatic illustration of lesion viewed from in front.

liver protruding through the diaphragmatic tear. Keene and Copelman[8] reported delayed herniation of the liver and gall bladder in a severely injured paratrooper, but symptoms occurred soon after the trauma. The present case (as well as most of the others previously reported) was not diagnosed prior to operation. It is presented to stress the importance of considering diaphragmatic herniation of the liver in the differential diagnosis of rounded masses contiguous with the right diaphragm. Diagnostic pneumoperitoneum with roentgenographic study could be expected to aid in making the diagnosis.

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UNUSUAL DIAPHRAGMATIC HERNIA WITH DISPLACED LIVER

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TRAUMATIC diaphragmatic hernia with displacement of the liver is of uncommon occurrence. Harrington reported a series of 430 diaphragmatic hernias of all types and only two had livers displaced within the thorax. One of his cases was similar to the one reported herein, in that the right side was involved. Our case presented a double hernia with a diaphragmatic tear and an additional intercostal hernia. Organs involved were the liver, gall bladder, and hepatic flexure of the colon.

CASE REPORT

Mr. O. A., a 59-year-old white man, entered the Veterans' Hospital March 25, 1950, with a complaint of right chest pain which had been present since World War I. The pain had been dull and constant, and during the last several months had been seemingly progressive. Inspiration and walking aggravated it. It had been accompanied by a second pain over the precordium during the last three months which was described as being mild. He had never had any ankle edema, but was troubled with a frequent dry cough. Inasmuch as he had been diagnosed as having tuberculosis in 1918, he was concerned that this disease might be the offender. Inconspicuously, he told of a stab wound in the lower right anterior chest which he received eighteen years ago and had healed promptly.

The family history and past history were irrelevant.

Physical examination revealed an obese male of the stated age weighing 190 pounds. He was not orthopneic, and appeared comfortable. The findings were essentially limited to the chest. There was dullness over the lower half of the right thorax, and no breath sounds could be heard there. The heart was not enlarged to percussion, and the sounds were normal. There was a healed stab wound in the right seventh anterolateral interspace which had a "mushy" feel, and presented a defect in the intercostal muscle. There was no venous distention and no peripheral edema.

Hematology studies preoperatively showed a red cell count of 4.36 million, white cells 6,650, hemoglobin 12.2 Gm., and a normal differential smear. The sedimentation rate was 3 mm. per hour. Urinalysis was normal. Five sputum examinations were negative for tuberculosis organisms. Three stools were negative for ova and parasites. Skin tests for blastomycosis, coccidiomycosis, histoplasmosis, and echinococcus were negative. Bromsulphthalein test of the liver showed 10 per cent retention in 45 minutes.

A roentgenogram of the chest showed a slightly lobulated mass in the entire lower half of the right thorax continuous with the diaphragm. The heart was moderately displaced to the left. Barium studies of the intestinal tract revealed a loop of hepatic flexure of the colon above the expected level of the diaphragm and anterior to the mass. A diagnostic pneumoperitoneum revealed some of the air to have ascended into the right thorax partially surrounding the mass. The roentgenologist interpreted the mass to be liver, but could not rule out a mass within the organ itself. Roentgenograms of the gall bladder revealed nonvisualization.

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Fig. 1.—Preoperative roentgenograms. Posteroanterior view shows pneumoperitoneum.

Fig. 2.—Postoperative roentgenogram with liver replaced and phrenic paralysis.

On April 25, 1950, the patient was explored through a right posterolateral incision over the bed of the seventh rib under endotracheal nitrous-ether-oxygen anesthesia. Three-fourths of the liver, including its entire right lobe, gall bladder, and hepatic flexure of the colon were found in the right thorax completely displacing all lung tissue from the lower half. Adhesions were dense but separated without difficulty. The liver and colon were returned to the abdomen, taking about five minutes to return the former organ by rotating and flexing it 90 degrees. No embarrassment to the heart was noted in this reduction. The right phrenic nerve was crushed, and the tear in the diaphragm sutured with interrupted silk. There was a 4-centimeter hernia in the seventh interspace where the colon had emerged at the stab wound scar. This was covered only by skin but was easily approximated by tacking the diaphragm against it. The lung expanded well and the pleural cavity was connected to an underwater trap by two right-angle drainage tubes. One thousand cubic centimeters of blood were given during the operation.

Fig. 3.—Operative findings—liver, gall bladder, and colon displacing lung through diaphragmatic and intercostal hernias.

Postoperative convalescence was uneventful. The patient was sitting in a chair on the second postoperative day and walking the third day. Within two weeks he remarked that he no longer was dyspneic and felt better than he had for years. No ventilation studies were done on this patient. He was discharged May 10, 1950.

DISCUSSION

The diagnosis of this case offered many problems. The presence of a seemingly lobulated mass in the lower thorax entails a differential diagnosis of tumors and cysts of the lung, liver, diaphragm, and mediastinum. The evidence of communication between the peritoneal and right pleural cavity was pure happenstance, and enhanced the effectiveness of the pneumoperitoneum in establishing the fact that this was a hernia. One normally expects to find a complete seal of the opening, particularly after many years have passed. Whether one was then dealing with a mass in the liver would depend on what the surgical exploration showed.

Symptoms in this case were limited to embarrassment of the cardiovascular system. The colon was not obstructed in its displacement. Although we did not have any preoperative diagnostic information on cardiac output, the patient demonstrated moderate dyspnea on exertion which was relieved by the operation. One can visualize the considerable impairment on the heart produced by the torsion and angulation of the inferior vena cava. The sedentary life of this patient probably helped him from evidencing any real cardiac failure.

Operative problems were overcome largely by (1) a thoracic approach, and (2) temporary relaxation of the diaphragm produced by crushing the phrenic nerve. Replacement of a large organ as the liver must be done gradually to obviate any severe taxation on the input to the heart. Suture of the large rent offers no problems if none of the atrophic muscle fibers of the diaphragm are sacrificed in the dissection. The intercostal hernia offered no technical problems and was more an interesting additional finding.

CONCLUSIONS

1. A traumatic hernia of the right diaphragm is reported which presented displacement of the major portion of the liver, gall bladder, and hepatic colon. It was accompanied by an intercostal hernia containing the loop of colon.

2. A liver displaced within the thorax can produce considerable cardiovascular impairment of function, and should be corrected early if possible.

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HOMOTRANSPLANTATION OF TRACHEAL SEGMENTS PRESERVED BY LYOPHILIZATION; AN EXPERIMENTAL STUDY

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THE use of tracheal homografts has been suggested as a possibility in repairing circumferential defects of the trachea. The application of such a procedure becomes apparent since resections of the trachea are feasible in the treatment of malignant disease primary in the trachea or secondarily affecting the trachea from adjacent structures.

Attempts to bridge defects in the trachea and primary bronchi by tubes of glass, stainless steel, or Vitallium has been attempted by Daniel.[1] He found that a viable tissue cover formed about the tube and in some animals, well-differentiated cartilaginous rings were formed in the developing tissue about the tube. Longmire[2] reported the use of a Lucite tube in repairing a tracheal defect in a patient with good results. Clagett and his co-workers[3] used Polythene tubes and most of the dogs did well, but in some instances the tubes came loose or collapsed. Successful autografts of segments of bronchus have been reported by Carter and Streider.[4] They also reported successful results with homografts, but in these cases stenosis of the bronchus was the great problem. Ferguson, Wild, and Wangensteen[5] have reported unsuccessful results at attempts to reconstruct short tracheal segments by means of autografts, homografts, aortic grafts, and tantalum gauze. However, these grafts were studied only for short periods of time.

Tracheal homografts can become feasible if methods are developed by which tracheal segments can be secured and stored in a relatively simple manner. The preservation of tissue by lyophilization was first suggested by Webster[6] in 1943. He attempted to transplant skin with poor results. In those tissues which can be transplanted successfully by host replacement, lyophilization is an ideal method of preservation because they can be kept at room temperatures for indefinite periods of time.[7]

The purpose of this experimentation was to determine the feasibility of lyophilizing tracheal segments to be used as satisfactory homografts in animals.

METHODS OF STUDY

Preservation of Tracheal Segments.—The tracheas to be preserved were taken from animals which had been sacrificed. They were placed in a lyophilizer, dried at a temperature of –15° to –25° C., and kept under vacuum (0.001 mm.) from seventy-two to ninety-six hours, removed, and placed in sealed jars. They were kept at room temperature until time of transplantation.

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Implantation of Tracheal Homografts.—Eight dogs were studied in this experiment. Under intravenous nembutal anesthesia, a linear incision was made in the midline of the neck, and the strap muscles were separated to expose the trachea. A portion of the trachea ranging from 2 cm. to 10 cm. in length was resected. A homograft of suitable size was hydrated with physiologic saline and sutured into place. Each animal was examined endoscopically at weekly intervals. Each animal was autopsied at appropriate intervals, and the site of transplantation examined.

Fig. 1.—Lyophilized tracheal homograft before hydration.

Fig. 2.—Dog No 4-10-50. Lyophilized homograft ten days after transplantation. Storage time thirty days.

RESULTS

Tracheal segments subjected to lyophilization are in all respects devitalized segments. They have the appearance of rigid tubes (Fig. 1). After hydration with physiological saline, they take on the appearance of normal tracheas.

Results of homotransplantation of lyophilized tracheas are summarized in Table I. There was no infection locally or in the mediastinum. Postoperatively all wounds of the trachea healed by primary intention. Endoscopically during the first two weeks postoperatively, marked congestion was noted in the area of the homograft. This increased vascularity decreased after the graft had healed and was not seen after three weeks. Healing occurred in all tracheal homografts except in one animal which developed pneumonia, and a severe necrosis was noted in the graft wall (Fig. 2). The grafts healed by replacement of the graft by fibrous connective tissue with loss of the cartilaginous rings (Fig. 3). In some instances, there was a tendency toward new cartilage formation within the graft. There was some torsion in the trachea noted, but no stenosis was noted in the grafted areas.

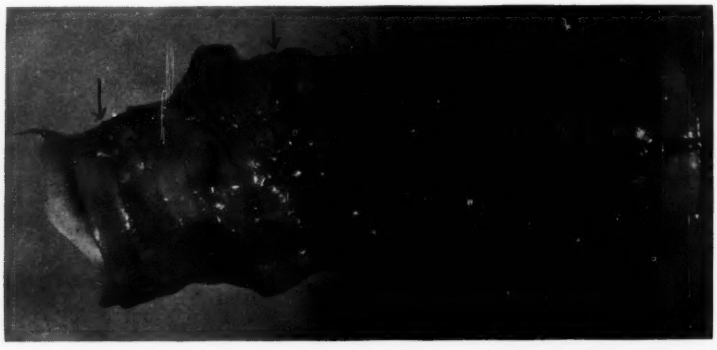

Fig. 3.—Dog No 4-20-50. Lyophilized homograft ninety days after transplantation. Storage time ninety days.

TABLE I. RESULTS OF TRANSPLANTATION OF LYOPHILIZED TRACHEAL HOMOGRAFTS IN DOGS

DOG NO.	LENGTH OF TIME GRAFT PRESERVED (DAYS)	LENGTH OF LIFE POSTOPERATIVELY (DAYS)	CAUSE OF DEATH	FATE OF GRAFT
4-1-50	10	8	Sacrificed	Excellent
4-5-50	20	15	Sacrificed	Excellent
4-10-50	30	10	Pneumonia	Necrosis of graft
4-15-50	60	30	Sacrificed	Excellent
4-20-50	90	90	Sacrificed	Excellent
4-25-50	120	90	Sacrificed	Excellent
4-30-50	15	90	Sacrificed	Excellent
5-1-50	8	120	Sacrificed	Excellent

DISCUSSION

In lyophilization, the tissue is dried in vacuum by reducing its water content as ice instead of evaporating it as a liquid. This process reduces it to its lighter and less bulky state, allowing it to be stored at room temperature without impairing its quality and value. The proteins are preserved in a dried state so that these transplants act in the same manner as fresh homografts or homografts stored in a refrigeration medium.

The healing of lyophilized tracheal homografts occurs by replacement of the graft by fibrous connective tissue. A slight necrosis occurs within the wall of the graft during the first two weeks, but this does not interfere with the ultimate healing of the graft. Epithelium regenerates along the lumen of the graft by replacement, and there is some tendency toward cartilage formation in its wall so that a satisfactory bridging is obtained.

Primary suture of the trachea as shown by Maisel and Dingwall,[8] Scott,[9] Nach and Rothman,[10] and Jackson and his co-workers[11] is superior to homografting. When extensive segments of the trachea are to be resected, homografts may be necessary to bridge such defects. Homografting is feasible only when grafts are preserved and can be used as satisfactory grafts.

CONCLUSIONS

1. The use of preserved homografts by lyophilization has been described.
2. The healing of lyophilized tracheal homografts takes place by replacement of the graft by connective tissue
3. Homografts may be necessary to bridge defects where extensive segments of trachea are resected.

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BRONCHIOGENIC NEOPLASM MASQUERADING AS ALVEOLAR CELL CARCINOMA

With Report of a Case Clarified Only by Autopsy

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SIGNIFICANCE of human alveolar cell tumor has been debated for years. According to Ikeda[26] and Neubuerger and Geever,[36] this condition was probably first described by Malassez in 1876 as encephaloid carcinoma. Since then a considerably widening nomenclature has developed; and now includes pulmonary adenomatosis, suggested by Drymalski, Thompson, and Sweany,[15] by Sims,[47] by Simon,[44, 46] by Richardson,[41] by Hildebrand,[25] and by Bubis and Erwin;[9] carcinosis, advocated by Bonne;[6] pulmonary mucous epithelial hyperplasia, favored by Taft and Nickerson;[49] diffuse primary alveolar carcinoma of the lung, advanced by Simon;[45] alveolar cell tumor, nominated by Neubuerger and Geever;[36] primary multiple alveolar cell tumor, proposed by Neubuerger;[35] and pulmonary alveolar adenomatosis, preferred by Wood and Pierson.[54] Both Ikeda[26] and, more recently, Delarue and Graham[14] have suggested the term alveolar cell carcinoma as most appropriate.

The number of published cases, regardless of title, exceeded seventy when recently tabulated by Simon.[45] But antemortem recognition was claimed for only three in this entire group, and solely by "microscopic examination of surgically obtained tissues," according to Weir.[51] However, the latter has also described an additional patient in whom aspiration biopsy was diagnostic, and considers this the first correct preoperative diagnosis ever reported for this condition.

After reviewing the literature, we shall discuss a further interesting case in which preoperative exfoliative studies, preoperative bronchoscopic biopsy, microscopic surgical specimen examination, and gross autopsy findings were all compatible with primary alveolar carcinoma. Unexpectedly, however, microscopic postmortem study revealed bronchiogenic malignancy, with pattern of metastasis entirely indistinguishable from that commonly described in alveolar cell tumor.

We consider such a report instructive for two reasons. In the first place, apparently all diagnostic criteria had been fulfilled before any surgical procedure was carried out. An even more important, our eventual findings appear to cast some doubt upon the possibility of pure alveolar carcinoma actually existing in primary form.

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CONTROVERSIAL PERSISTENCE OF HUMAN ALVEOLAR EPITHELIUM

Although alveolar epithelium is usually considered prerequisite to development of primary tumor in this location, embryologists and pathologists do not completely agree concerning its persistence after the fifth fetal month.

Bell[5] believes that partial disappearance at that time assists in future oxygen-blood interchange, but feels that certain cells survive and may subsequently form a continuous layer under proper stimulation. He has seen evidence of the latter in chronic passive pulmonary congestion, and lipid pneumonias, and states that hyperplasia may "arise by multiplication of pre-existent alveolar epithelial cells, and not as an ingrowth of bronchial epithelium." Wood and Pierson,[54] Ikeda,[26] Casilli and White,[10] and Miller[32] also agree; the latter states that "evidence points to a continuous epithelium lining the pulmonary alveoli."

In further confirmation, it is recalled that Slye, Holmes, and Wells[48] reported spontaneous development of alveolar tumors among mice in 1914. Murphy and Sturm[34] produced similar lesions after application of coal tar distillates to the skin. Subsequently Grady and Stewart[20] reduplicated these findings among inbred strains by subcutaneous injections of 1, 2, 5, 6—dibenzanthracene; it seems unlikely that any of these animal tumors would have developed unless alveolar epithelium was originally present.

Fried[16] considers that human bronchopulmonary carcinoma arises from alveoli, bronchial mucosa, or bronchial glands; and, therefore, accepts the fact that alveolar epithelial cells persist after birth. Cooper[11] and Karsner[30] agree with the latter conclusion, although Karsner concedes that exact cellular structure is not clear. Neubuerger and Geever[36] have demonstrated persisting alveolar epithelium in certain chronic pulmonary conditions such as silicosis and tuberculosis, and following irritation by chemicals, oils, gases, and toxins. They also refer to Brachet's concept that *all* germ layers may develop unusual reactions after stimulation; the latter possibility, if confirmed, would permit development of neoplasm from pulmonary mesenchyme alone.

Among those opposing survival of alveolar epithelium, Herbut[22] is perhaps the most emphatic. Basing his conclusions upon study of selected cases from 6,500 consecutive autopsies, he asserts that apparent alveolar hyperplasias are actually due to downgrowth of encroaching bronchial mucosa, and can always be shown to merge with the latter by careful study; both he and Frissel and Knox[17] feel that true bronchiogenic carcinoma may reproduce the exact peripheral pattern often described as primary alveolar tumor. Arkin and Wagner[3] consider all pulmonary carcinoma bronchiogenic, and feel that malignancy cannot derive from alveoli, since the latter retain no persistent epithelial lining. Neubuerger,[35] Barnard and Day,[4] and Geever, Neubuerger, and Davis[18] are satisfied that alveolar epithelium disappears before birth, that it does not reappear in adult life, that replacement is made by mesenchymal septal cells and capillaries, and that carcinoma cannot develop from mesenchyme. Ham and Baldwin[21] classify alveoli as "merely spaces in tissue derived from cellular mesenchyme" and therefore incapable of originating tumor. Moore,[33] Weller,[52] and Jordan and Kindred[29] find little evidence of residual adult epithelium, while

D'Aunoy, Pearson, and Halpert[13] give such negligible consideration to the latter's survival that the alveolus is not even mentioned as a possible site of lung tumor.

Other investigators have been in doubt. Macklin[31] summarized a round table discussion among various authorities in the middle '30s, from which no definite conclusions were forthcoming, one group feeling that a complete lining persisted, although possibly invisible to usual means of examination in normal tissue, another group accepting evidence of occasional residual surviving cells, while a third group was convinced of complete disappearance and permanent replacement by mesenchyme.[31] Taft and Nickerson[49] concede the possibility of adult epithelium, but do not entirely exclude a bronchial source; Boyd[7, 8] believes all reported alveolar hyperplasias are probably bronchial in origin, while Jaffe,[28] Anderson,[2] and Herbut[23] are undecided.

One is therefore faced with lack of complete agreement concerning postnatal alveolar epithelium. Unless he accepts proof of the latter, he cannot reasonably hold that primary alveolar tumor may develop therefrom. However, since a persisting membrane has definitely been reported by several authorities,[32 et al.] it does appear to us that included cells are capable of providing the necessary framework for localized hyperplasias, and perhaps even malignancy.

ETIOLOGY OF ALVEOLAR METAPLASIAS

In the preceding section, various investigators have been indirectly quoted in reference to carcinogenic properties of certain irritants, and to probable stimulating effects of chronic pulmonary diseases, in production of alveolar hyperplasias. Richardson,[41] while doubting frequent involvement of this type, agrees that occasional lesions may range from incidental autopsy findings to pathology sufficient to produce death.

In further confirmation, Seelig and Benignus[43] have found that inhaled chimney soot could produce generalized pulmonary carcinoma in cancer-sensitive mice; while, among a genetically resistant strain, pure alveolar involvement was suggested. In 1920, Winternitz, Smith, and McNamara[53] stimulated alveolar proliferation in rabbits by insufflation of 0.25 per cent HCl, as a result, alveoli developed an entirely new epithelial layer, similar to that seen after influenzal pneumonias, but involving bronchi as well. Young[55] has demonstrated related alveolar changes after intrapleural irritation by paraffin, bile, and other salts. Ikeda[27] created circumscribed nodular pulmonary lesions in rabbits through tracheal administration of various liquids; by use of cod liver oil, for example, alveolar epithelization was demonstrated within two weeks. Furthermore, Norris[37] discovered comparable changes in guinea pigs after inoculation of fluid aspirated from a patient with pneumococcus pneumonia, and quotes identical results achieved by Grumbach through use of diphtheroid bacilli recovered from a patient with Hodgkins disease. Related, although unexplained, findings have also been reported in mice and horses, according to Bubis and Erwin.[9]

Although Frissell and Knox[17] do not accept proof of alveolar carcinoma, they have conceded that metaplasia in immediately adjacent bronchial mucosa may result from various irritations; the latter seem to include influenza, war

gas, tuberculosis, products of tar and cigarette combustion, radioactive mine dusts, and others. Heuper[24] does not restrict possibility of such changes to the bronchus, and in 1950 concluded that identical pathology might also occur within the lung field itself.

These various investigations, therefore, suggest that significant changes in alveolar membranes may well occur after specific irritation. And perhaps most likely, as intimated by Delarue and Graham[14] in referring to Andervont's observations in mice, in those with genetic tendency to such. This factor of predisposition and susceptibility is also emphasized by Ikeda[26] and Alexander and Chu,[1] who relate it to a chain of progressive abnormalities consisting of (a) hyperplasia, (b) benign adenomatosis, and (c) alveolar carcinoma. No evidence yet incriminates viral etiology in human malignancy of the latter type, although a virus is apparently responsible for Jaagziekte, an ovine illness in many ways similar to alveolar cell tumor in man.

Jaagziekte has variously been described as epizootic adenomatosis, pulmonary adenomatosis of sheep, verminous pneumonia, and progressive pneumonia of sheep. First reported by Eber in 1891,[47] and originally considered by M'Fadyean to be caused by parasitic lung worms, it is now endemic in South Africa, Iceland, England and the Rocky Mountain regions in and about Montana. Cowdry,[12] in 1925, eliminated spirochetes, nematodes and coccidiosis as responsible agents; and today a virus etiology is generally accepted. Incidentally, no authenticated instance of transmission from sheep to shepherds has yet been described.[44]

Characteristic histopathological structure in Jaagziekte closely simulates that seen in human beings reported dying of alveolar cell carcinoma. It includes multicentric pulmonary foci; tumorlike reproduction of alveolar structure with columnar, occasionally papillary, and nonciliated cells; relative absence of mitosis; and general infrequence of stromal invasion. The lung pattern, according to Geschickter and Dennison,[19] duplicates that seen in mice after cutaneous coal tar applications. Metastasis, discovered in about 50 per cent of cases labelled human alveolar carcinoma, has been reported only once in Jaagziekte,[54] however.

Although difficult to transmit artificially, Jaagziekte appears to spread with great rapidity when healthy sheep are confined with infected flocks. Dungal, according to Wood and Pierson,[54] suspected that individual susceptibility varied according to genetic strain of the herd involved; this observation might further explain spotty and unpredictable development of somewhat similar alveolar tumors in man. It is not surprising, therefore, that numerous investigators have postulated a relationship between Jaagziekte and human alveolar carcinomatosis, although a virus does not appear to be the responsible agent in the latter condition.

PATHOLOGY OF CASES DESCRIBED AS ALVEOLAR CELL CARCINOMA

Those[36, 26, 45, 15, 54, 46, 14, 51 et al.] who have reported autopsied cases agree generally upon gross and microscopic findings. Both a diffuse form, first mentioned by Musser in 1903,[36] and a multiple nodular type are described, each usually occurring in the same individual, and often in the same lung.

Grossly, the diffuse lesion resembles gray hepatization in pneumococcus lobar pneumonia, and may well represent confluence of original discrete nodular densities. The latter consist of multiple, miliary to marble-sized, yellow to pinkish-gray, firm tumor masses; and are either discrete, fused, or necrotic. Intervening parenchyma may appear grossly intact, or be involved in hyperemia and pneumonia of variable degree. The visceral pleura is at times invaded by tumor, and a pleural effusion, occasionally bloody,[26] has been described.

Microscopically, the essential finding is that of exuberant reduplication of alveolar pattern; nonciliated columnar cells may appear in multiple layers or show a tendency to papillary formation with little evidence of mitosis, and are said clearly to differ from those seen in bronchiogenic adenocarcinoma.[26] Since the tumor is frequently described as lying within alveoli in detached sheets, one wonders if it might not more often be detected by intensive exfoliative sputum or bronchoscopic aspiration studies. According to Simon,[45] appearance of the responsible cell is "so unlike the ordinary bronchiogenic carcinomas as to suggest at once that the tumors are different." A further invariable finding is said to be that of lack of involvement of major bronchi, unless by ulcerative invasion or direct extension.[10, 35, 36, 44, 45, 26, 15, 54 et al.] Absence of stromal invasion is also almost constantly described.

In addition to distinctive alveolar pattern and absence of primary tumor in bronchial mucosa or elsewhere, a third identifying characteristic of alveolar cell tumor appears to be its multicentric origin.[36, 10, 54, 16, 26, 14 et al.] Formerly, all malignancies were thought to arise in one location; however, in 1921, Owen[40] suggested this might be in error. Several years later, Orr[38] proposed the theory of multiple genesis, and in 1934 Schreiner and Wehr[42] reported 2.7 per cent of malignancy autopsies showing multicentric primary tumor sites. Warren and Gates[50] concluded in 1932 that such a finding was no longer a pathologic curiosity, that it occurred more frequently than could be explained by chance, and that it might be related to systemic predisposition or continued action of some irritating factor favoring widespread malignant change.

In spite of this, however, multicentric origin is not a characteristic of carcinoma of the usual bronchiogenic type, and its demonstration in tissues described as showing alveolar cell tumor is said to be a distinctive differential point. Those who favor alveolar cell carcinoma as a definite clinical entity also state that a primary lesion elsewhere is always excludable, and that metastasis cannot therefore explain multiple pulmonary involvement. Herbut,[22] however, reports he is frequently able to identify a responsible primary bronchial lesion by close microscopic study, providing it has not been lost to view through metastatic invasion. Simon[45] dismisses the latter observation since, in seventy reported autopsies, he feels that sixty other pathologists would have discovered primary malignancy elsewhere, if actually present. In our patient, however, as in several of Herbut's,[22] such was microscopically apparent.

As stated previously, metastasis has been described in slightly more than 50 per cent of all cases of alveolar carcinoma.[45, 36] Neubuerger[36] considers half

will show involvement of hilar and bronchial nodes alone; while, in the remainder, the liver, remote lymph nodes, kidneys, brain, adrenals, and pericardium are invaded in that order. It has been reported that the microscopic pattern of metastasis clearly reduplicates that of the primary alveolar tumor. In one unusual case reported by Wood and Pierson,[54] in which malignancy of the cervix was a complicating finding, two distinct types of pulmonary invasion were differentiated by the pathologist; one associated with alveolar neoplasm, and a second metastatic form clearly related to uterine origin.

SYMPTOMATOLOGY, DIAGNOSIS, PROGNOSIS, AND TREATMENT

There is no apparent symptom complex directly suggesting the condition described as human alveolar cell carcinoma. In one of three autopsied cases reported by Ikeda,[26] the patient was without lifetime respiratory complaint; while, in another, the latter developed only a month ante mortem. Weir[51] reports that most patients show a healthy appearance until shortly before death. Cough is usually present, often at first dry, but subsequently productive of copious quantities of clear frothy sputum. Dyspnea and loss of weight have frequently been noted, although hemoptysis is rare.[1] Duration of complaints ranges from a few weeks to years; although, in retrospect, numerous patients will admit attacks of "pneumonia" and "pleurisy," in association with progressive physical decline.

Little specific diagnostic assistance may be expected from roentgenogram or laboratory studies, except those related to exfoliative sputum examination and occasional needle biopsy; Weir,[51] as noted previously, has reported accurate recognition in a single instance, following the latter procedure.

Prognosis is decidedly poor and treatment usually ineffectual, the majority succumbing to suffocation before correct diagnosis is made. However, Delarue and Graham[14] report one case with freedom from symptoms for more than three years post-lobectomy, although with subsequent recurrence. They also cite an apparent two-year postoperative cure in a patient of Osserman and Neuhof, whom the latter[39] have now followed for five years, who remains symptom-free, and whose chest film is clear at this time. Incidentally, the neoplasm described as alveolar cell carcinoma is apparently not radiosensitive.[51]

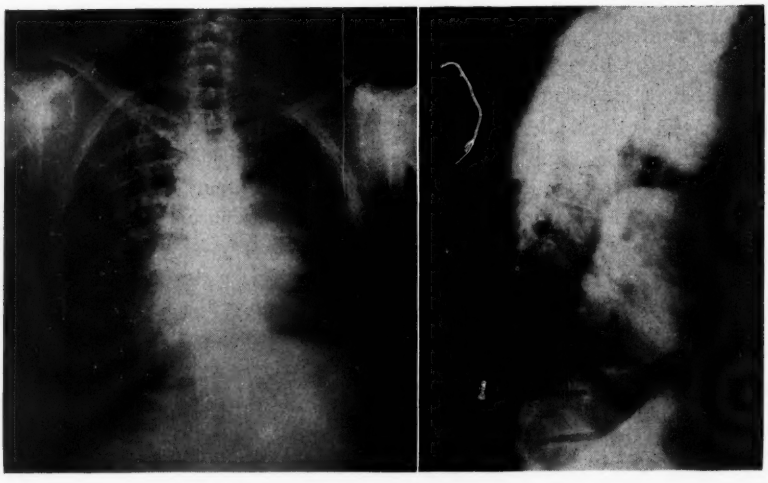
REPORT OF A CASE

C. K., a 45-year-old white native-born Ohio farmer, had recently been employed as a motor assembler. Twelve years previously many of his sheep had succumbed to an illness characterized by "destruction of the eyes"; however, no classical respiratory symptoms were noted in these animals, and he lacked contact with known diseased herds since that time. His father died of "asthma," and one brother of influenza; his wife, mother, and six siblings were living and well at the time of hospitalization. A 12-year-old daughter showed roentgenogram evidence of healed primary tuberculosis, with positive tuberculin test.

Three years previously the patient had fallen down stairs and "injured his back." Some time later, he began to note progressive weakness and weight loss, complicated by nonproductive cough. He sought no medical advice until August, 1949, when, because of chest pain, he visited our clinic. Roentgenogram disclosed right pleural effusion (or empyema)

overlying an apparently consolidated or atelectatic right lung; contralaterally, a diffuse soft infiltration was seen. Although two sputum examinations failed to reveal tubercle bacilli, provisional diagnosis of pulmonary tuberculosis and pleurisy with effusion was made. Hospitalization was accepted Dec. 19, 1949.

Fig. 1.—Hospitalization chest film, Dec. 20, 1949.



A. *B.*

Fig. 2.—Posteroanterior and lateral chest films after thoracentesis. *A*, Feb. 1, 1950; *B*, Jan. 23, 1950.

The patient was moderately febrile on admission, but without significant respiratory complaint. Painless facial twitching was apparent; right Babinski and bilateral Oppenheims were present. Sensation was normal. No lymphadenitis was discovered, although liver edge and splenic tip were palpable. The thorax was asymmetrical, with right-sided lag. Pulmonary

physical findings were consistent with right pleural effusion or empyema, while râles were audible throughout the left chest only. The heart was of normal size, shape, and position; without irregularity, but with simple sinus tachycardia. A soft, nontransmitted mitral systolic murmur was not associated with palpable thrill. Blood pressure was 120/80. Vital capacity 1,300 c.c. or 33 per cent of anticipated normal.

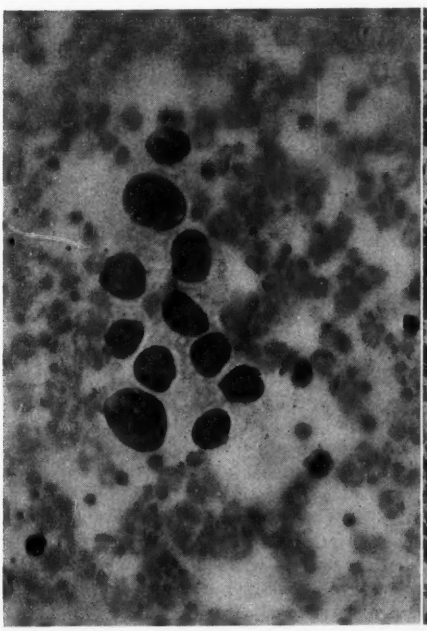


Fig. 3.

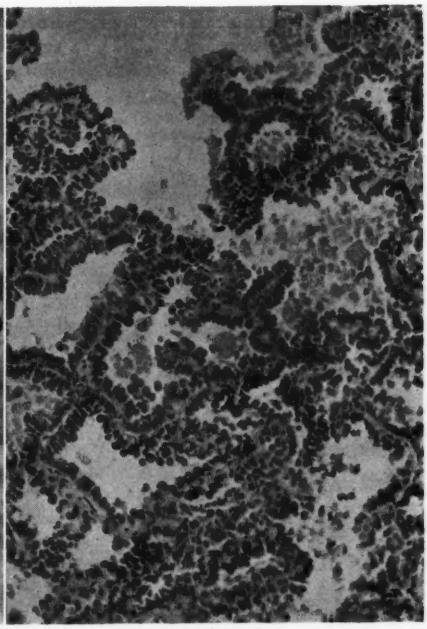


Fig. 4.

Fig. 3.—Exfoliative study of bronchoscopic aspirations.
Fig. 4.—Biopsy from lower lobe bronchus, Jan. 11, 1950.

Admission roentgenogram suggested right-sided tuberculous or nontuberculous pathology (possibly malignancy complicated by right pleural effusion or empyema) and a progressing contralateral lesion (Fig. 1). Old Tuberculin was positive (1:10000 dilution); histoplasmin and coccidioidin skin tests were negative. Concentrated sputum examination failed to reveal tubercle bacilli. A mild macrocytic (MCV 111), normochromic (MCH 32) anemia was present. White blood count totalled 10,400, with 75 polymorphonuclears (of which 73 were segmented forms), 12 lymphocytes, 10 monocytes, 1 eosinophile, and 2 basophiles. Sedimentation rate was not accelerated; urinalysis showed no abnormality; serology was negative.

Certain further diagnostic procedures then carried out may be summarized as follows:

(a) *Multiple thoracenteses*: Thin wine-colored fluid was aspirated on numerous occasions. Tubercle bacilli were absent by concentration in eight specimens, by culture in eight, and by animal inoculation in three. No other organisms were cultured in six examinations. Eight fluid specimens failed to show neoplastic cells. Specific gravity varied between 1.022 and 1.028, protein between 150 mg. and 5 Gm. Cells ranged from 1,350 to 3,400 per cubic millimeter; of these, polymorphonuclear forms fluctuated between 58 and 72 per cent, with the remainder largely lymphocytes. Sugar was variously reported between 8 and 35 mg. per cent.

After thoracenteses, subsequent chest films showed a compact right lung of rounded contour (Figs. 2*A* and 2*B*).

(b) *Sputum studies*: Seven subsequent concentrated sputum specimens failed to show tubercle bacilli, with five negative colonial and two negative animal confirmations. However, a preterminal specimen of March 17, 1950, showed an occasional acid-fast rod, morphologically resembling the tubercle bacillus, confirmed by culture, but failing to produce tuberculosis in the guinea pig.

(c) *Spinal fluid*: Clear fluid was twice drawn under normal dynamics. Cell count, protein, sugar, chlorides, gold curve and serology were not abnormal. One culture and two animal inoculation studies failed to identify tubercle bacilli or other bacteriologic abnormality.

(d) *Admission bronchoscopy* revealed minimal proliferative tumefaction in a right lower lobe bronchus spur. A specimen was removed and secretions were aspirated for cytologic study. The latter showed "abnormal cells having large medium staining nuclei, with prominent nuclei and a relatively small amount of cytoplasm" (Fig. 3). Bronchoscopic biopsy disclosed an "epithelial neoplasm made up of columnar cells arranged in alveolar grouping and supported by a minimal amount of stroma. The cells are fairly regular in distribution and arrangement, but show loss of polarity and have large dark-staining nuclei of varying shape" (Fig. 4). This was considered compatible with malignancy of the alveolar carcinoma type.

(e) *Neurological consultation*: Because of continual facial twitching and lower extremity pain, neuropsychiatric consultation and spinal roentgenograms were requested. The neurologist found no cranial nerve disturbance, noted absence of sensory abnormality, but reported exaggerated deep reflexes. Twitchings were considered due to myoclonia or chorea, without evidence of diffuse or localized primary or metastatic cerebral lesions. Spine films showed no bony metastatic or soft tissue abnormality, and offered no explanation of lower extremity pain. The latter was also an unexplained finding in a case reported by Neubuerger[35] in 1941.

(f) *Miscellaneous studies*: An electrocardiogram was normal. Values for sugar, cholestrol, total protein, albumin-globulin ratio, nonprotein nitrogen and prothrombin times were within normal limits. Sodium was slightly, and potassium definitely, lowered; the latter to 8 mg. per cent. Repeated urinalysis and a phenolsulfonphthalein excretion test showed no abnormality.

Subsequent course.—

Under a working diagnosis of alveolar cell carcinoma, subsequent sputum study disclosed abnormal cells "reasonably similar to those seen in previous material from this patient" (Fig. 5). Bronchoscopic aspirations twice failed to reveal tubercle bacilli by culture and animal inoculation. Finally, on Feb. 2, 1950, the right chest was explored by Dr. M. G. Buckles both in confirmation of diagnosis and possibly for pneumonectomy.

Thoracotomy revealed a completely collapsed right lung, of the consistency of sponge rubber, covered by shaggy fibrinous exudate and bathed in serosanguineous fluid. The visceral pleura was quite dense and stripped with considerable bleeding. Pneumonectomy appeared both technically difficult and inadvisable. After resection of an upper lobe segment for microscopic study, the residual lung was found entirely unreexpandable following localized decortication. The chest was closed and the patient returned from the operating room in satisfactory condition. Aspirations removed bronchoscopically at time of surgery revealed further recognizable tumor cells.

Histpathologic study of resected tissue identified "large portions of a papillary epithelial neoplasm made up of columnar cells showing pseudostratification and having large dark-staining nuclei" (Fig. 6). This architecture was considered compatible with alveolar carcinoma.

Following surgery, the patient's condition remained fairly satisfactory for some time, with few or no respiratory complaints in evidence. This in spite of chest roentgenograms showing further progression throughout the left lung field, in association with a relatively

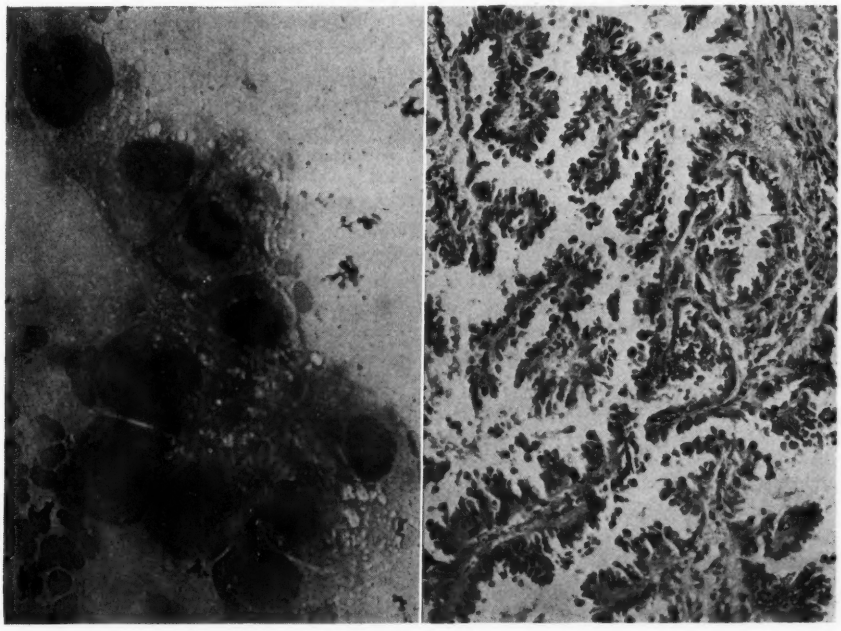


Fig. 5. Fig. 6.

Fig. 5.—Exfoliative study of pre-operative sputum, Jan. 30, 1950.
Fig. 6.—Section study of resected upper lobe, Feb. 2, 1950.

Fig. 7.—Chest roentgenogram taken shortly before death, April 11, 1950.

functionless right lung. After further aspiration of beer-colored fluid, a recheck roentgenogram April 11, 1950, revealed marked increase in contralateral nodularity and coalescence (Fig. 7). From this point, the patient steadily declined and, following onset of severe terminal dyspnea and cyanosis, expired May 12, 1950.

Autopsy.—

Unfortunately, permission to examine the head could not be obtained. Essential postmortem findings follow:

Gross Examination.—

Description of the Body.—The body was that of a short, slight, fairly well-developed and poorly nourished adult white male. There was a very well-healed, scarcely visible, operative scar in the lateral portion of the right chest. No other external abnormality was noted.

Thoracic Cavity: The right lung was partially collapsed, of rounded outline, and of very firm consistency. The parietal pleura was extremely thick and fibrous. The pleural cavity was filled with a thick mass of firm brown degenerating and organizing blood clot. It further contained a small amount of thick dark red unclotted blood. The left lung was of normal size, but very dense consistency. It was quite solid, and could be elevated for inspection only with difficulty. The pericardial sac was normal in size and location. Pericardial fluid was normal in character and amount.

Abdominal Cavity: As the abdomen was incised, considerable thick dark red unclotted blood escaped. Massive soft granular white neoplastic tissue was found on the under surface of the diaphragm, the upper surface of the liver, and in the form of multiple large masses throughout the omentum. The amount of peritoneal hemorrhage probably equaled half a pint.

Organs of Thorax.—

Esophagus: As the esophagus was opened, a rounded bulging mass was found distorting it and pushing into it. The mass was egg-shaped, measured about 4 by 1½ cm., and lay on the posterior right lateral border of the esophagus. It lay between the esophagus and the right lung. It had produced indentation of the right lung due to compression. The mass could be easily dissected from all surrounding tissue. It was found to be filled with thick white semimucoid liquid. Otherwise the esophagus was normal.

Trachea and Bronchi: The mucosa was hyperemic. The bronchi of the right lung were narrowed, particularly in the lower lobe. No recognizable tumor tissue could be seen from inside the bronchus.

Right Lung: This was decreased in size, the lobes were of rounded outline. The pleura was thickened. The pulmonary tissue was quite solid. The surface of the lung was covered with a mass of degenerating and organizing blood clot. The parietal pleura was very prominently thickened. The cut surface of the right lung presented a uniform solid, moist, gray cellular appearance (Fig. 8). The lung was cut in multiple transverse slices throughout its extent, and neoplastic consolidation was found to be uniform, homogeneous, and complete. The tumor appeared to surround bronchi, and gave no evidence of involving, or of springing from, bronchi.

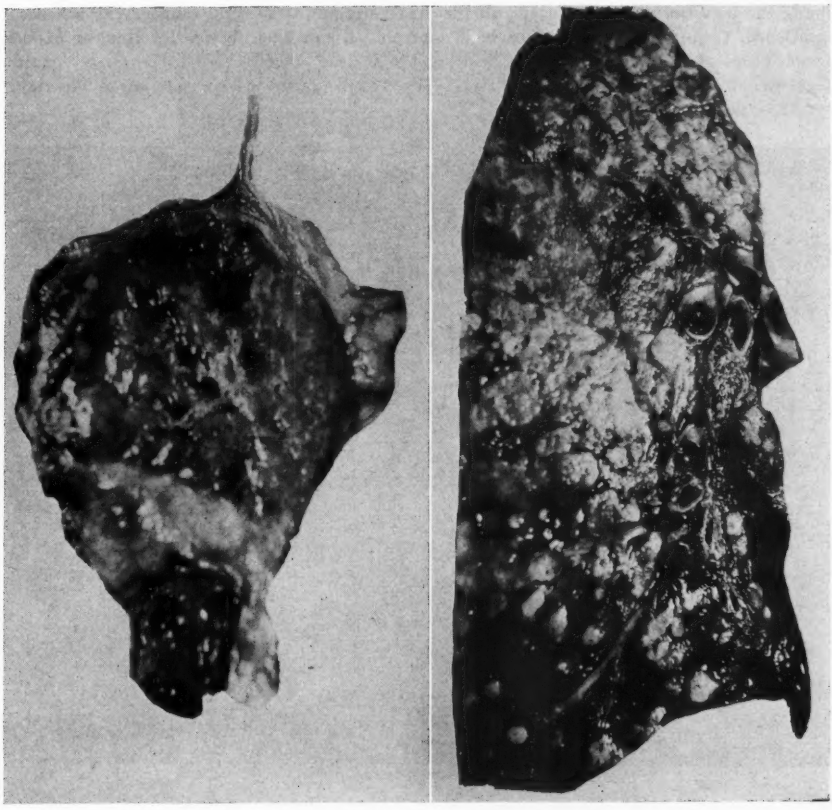
Left Lung: This was normal or increased in size. It was normal in shape and outline. The upper lobe was fairly diffusely consolidated, and the lower lobe contained multiple nodules of consolidation which tended to be confluent at times. The cut surface showed diffuse moist gray consolidation of the upper lobe, identical in appearance with that found in the right lung. The upper division of the lower lobe presented similar diffuse consolidation, but in lower portions of the lower lobe the consolidation was of scattered nodular distribution (Fig. 8).

Lymph Nodes: There was no gross evidence of involvement of hilus lymph nodes.

Heart: This was normal in size and shape. The external surface was smooth. The chambers were normal in size. The valve rings were normal in diameter. The endocardium was smooth. The myocardium was normal in thickness. Coronary arteries and aorta showed no abnormality.

Organs of Abdomen.—

Spleen: This was of average size. The external surface was smooth. The cut surface showed no abnormality, and was of a deep red appearance.



A. *B.*

Fig. 8.—Photograph of lungs in cut section after removal. *A*, right lung; *B*, left lung.

Adrenals: Both adrenals were large and nodular, and on section were found to be almost completely replaced by neoplastic tissue.

Kidneys: These were normal in size and shape. They cut with the usual degree of resistance. The markings were normal in appearance. The cortical tissue was normally thick. The pelves and ureters were normal. The capsules stripped easily, leaving smooth surfaces.

Bladder and Prostate: The bladder was normal in all respects. The prostate showed no abnormality.

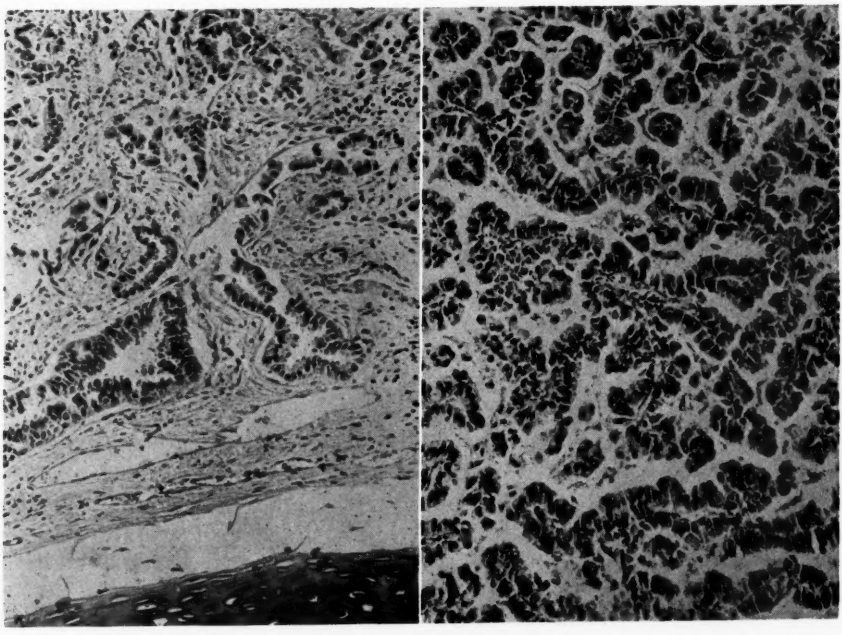
Testes: Normal.

Liver: The surface, particularly of the upper portion, was covered with neoplastic nodular tissue. There were some subcapsular areas of white neoplastic tissue. The cut surface showed a rather small number of small-sized scattered round white neoplastic nodules. These averaged about 3 mm. in diameter. Most neoplastic involvement of the liver was capsular. The gall bladder and bile ducts were normal.

Pancreas: Normal.

Gastrointestinal Tract: No abnormality was noted in the stomach or intestine.

Retroperitoneal Tissues: The neoplastic extension through the diaphragm, and to the undersurface of the diaphragm, extended down on the anterior surface of the peritoneum lining the posterior abdominal cavity in the area anterior to the right kidney. As has been mentioned, there was involvement of both adrenals. There likewise was involvement of the lymph nodes of the retroperitoneal area along the aorta. There seemed to be fairly definite involvement of the left sympathetic trunk. Involved lymph nodes lay anterior to the right sympathetic trunk.



A. *B.*

Fig. 9 *A* and *B*.—Microscopic section appearance of bronchial mucosa and parenchyma of right lung.

Thyroid: The thyroid gland was normal.

Anatomical Diagnosis.—

1. Diffuse lobar consolidation of entire right lung and upper lobe of left lung, with confluent lobular consolidation of lower lobe of left lung, by an alveolar carcinoma of pulmonary origin.
2. Neoplastic extension through diaphragm, with peritoneal and omental involvement.
3. Neoplastic involvement of adrenals and retroperitoneal lymph nodes.
4. Metastatic neoplastic lesions of liver.
5. Old organizing right hemothorax.
6. Recent hemoperitoneum.

MICROSCOPIC EXAMINATION

Lung: Several sections from the lower lobe of the right lung disclosed extensive alteration of bronchi by neoplastic tissue. The lumens were narrowed. The normal mucosa was replaced by a mass of neoplastic tissue. Neoplastic tissue streamed through the wall and diffusely into surrounding lung tissue. Microscopically these findings were rather typical of those ordinarily seen in bronchiogenic carcinoma (Fig. 9*A*). In the area of the replaced bronchial mucosa the tumor tended to be of an adenocarcinomatous structure. As it spread into the surrounding tissue it became of an alveolar type, into which there were frequent papillary projections. Groups of such alveoli were separated by fairly regularly distributed

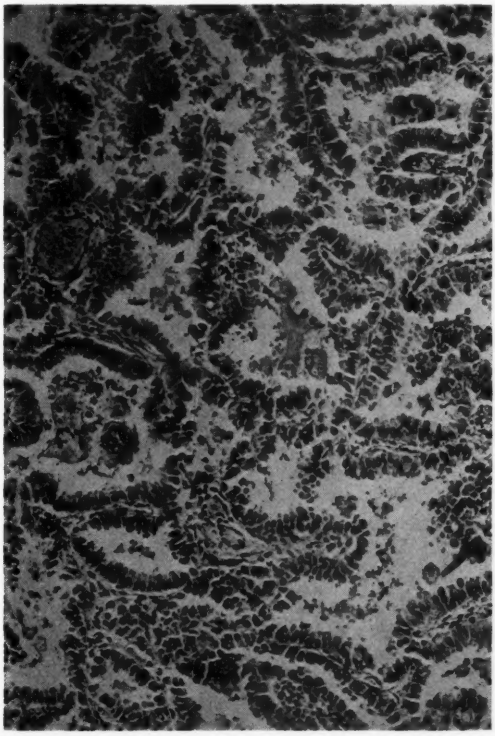


Fig. 10.—Microscopic section appearance of left lung.

interlobular septa (Fig. 9*B*). Sections from the left lung disclosed lobularly distributed masses of similar appearing tissue, separated by some uninvolved lung tissue which was the site of extensive congestion and edema (Fig. 10). Sections from the left lung did not show bronchial involvement. The distribution of these tumor cells afforded ample justification for employment of the term "alveolar carcinoma." However, their apparent origin from bronchial mucosa in an area with the usual pattern of an adenocarcinoma suggested that the alveolar arrangement was a type or variant of adenocarcinoma of bronchiogenic origin, rather than a primary tumor of alveolar epithelium.

Mediastinal Cyst: The cyst found between the esophagus and the hilus of the right lung was lined with ciliated columnar epithelial cells of the type ordinarily found in trachea and bronchi. These formed spaces extending into smooth muscle bundles apparently represent-

ing the wall of the esophagus. Extending tumor tissue from the neoplasm of the right lung was found in close proximity, but this appeared to be coincidental.

Heart: Coronary vessels showed minimum sclerosis. The epicardium was normal, myocardial fibers were of normal size and staining reaction.

Spleen: Normal.

Adrenal: There was extensive metastatic neoplastic tissue quite similar to that seen in the lung and tending to maintain the same alveolar distribution of cells. There was extension and infiltration into the surrounding fat and fibrous tissue where the pattern was more akin to that of the usual adenocarcinoma (Fig. 11).

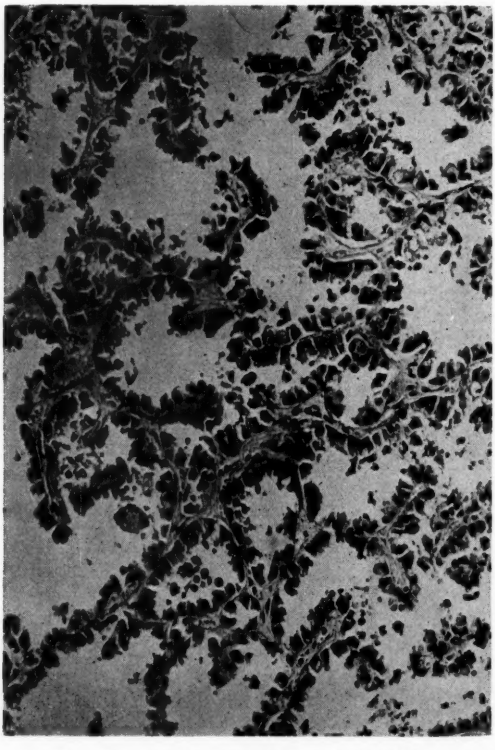


Fig. 11.—Appearance of adrenal metastasis.

Kidney: There was no evidence of neoplastic involvement. The general architecture, blood vessels, and glomeruli were normal. Tubules were normal or showed slight epithelial degeneration.

Prostate: Normal.

Liver: Hepatic cells were extensively shrunken with resultant widening of sinusoids. The liver contained an area of tumor tissue similar to that seen elsewhere, including some portions with alveolar grouping.

Pancreas: Normal.

Thyroid: Normal.

Sympathetic Ganglia: There was extensive neoplastic infiltration.

Microscopic Diagnosis.—

1. Bronchiogenic adenocarcinoma giving rise to diffuse alveolar carcinoma of lung, with metastases to adrenals, liver and retroperitoneal structures.

2. Bronchiogenic mediastinal cyst.

FINAL DIAGNOSIS

1. Bronchiogenic adenocarcinoma of lower lobe of right lung with diffuse alveolar carcinoma of right and left lung, and with extension through diaphragm involving peritoneum and omentum, adrenals, sympathetic ganglia and liver.

2. Old organizing right hemothorax.

3. Recent hemoperitoneum.

4. Bronchiogenic mediastinal cyst.

DISCUSSION

In spite of difference in opinion concerning persistence of human alveolar epithelium after the fifth fetal month, there is consensus that certain cells persist in relic form and, after irritation and stimulation, may readily be demonstrated. Especially following pneumonias, during passive pulmonary congestion, and in other conditions where edema separates the alveolar membrane from surrounding structures and aids in its identification.

Debate has naturally arisen over the possibility of discovering primary tumor in this area, with most investigators apparently feeling that carcinogens and irritants may occasionally produce a localized neoplastic change. Such is known to occur in laboratory animals, and similar irritation is also generally accepted as partially responsible for human carcinomas of the bronchiogenic type. Furthermore, sheep may develop a somewhat parallel alveolar lesion known as Jaagziekte, presumably caused by a virus, but apparently most frequently seen in flocks with genetic predisposition to such.

Although more than seventy cases of human alveolar cell carcinoma have been described under varying nomenclature, Herbut and others do not believe the tumor is primarily alveolar in origin and feel they have demonstrated direct communication between a responsible bronchial site and involved alveoli. Those favoring primary alevolar tumor as an actual clinical entity, however, point out certain characteristics which are said to clearly distinguish it from all other malignancies. These include (a) reduplication of alveolar pattern by cells whose morphology differs entirely from that of bronchiogenic carcinoma, (b) failure to identify primary neoplasm elsewhere, and (c) multicentricity.

With these criteria as a guide, our patient was considered to have primary alveolar cell carcinoma throughout most of his hospital residence. This impression was supported by sputum and bronchoscopic exfoliative studies, bronchoscopic biopsy, postresection specimen examination, and gross autopsy findings. He showed the reported lack of agreement between respiratory symptoms and extreme pulmonary involvement by roentgenogram; tuberculosis and extrapulmonary malignancy were apparently excludable; multicentric lesions, both of the diffuse nodular and massive consolidative types, were suggested by a variety of examinations. In short, until postmortem section study was completed, this

case very closely simulated others reported as authenticated primary alveolar carcinomas; and, also important, was one in which diagnosis had apparently been made by us before any operative procedure was offered.

Lower extremity neuritis was a clinical finding not clearly understood during this patient's life but, in view of autopsy studies, can now be ascribed to retroperitoneal metastasis and involvement of major nerve trunks. Identification of nonpathogenic tubercle bacilli in a single preterminal sputum specimen was considered a "red herring," since we have seen four hospital cases in the past three years with an identical finding, but without evidence of clinically significant tuberculosis by autopsy.

Microscopic autopsy sections were crucial in this case. They disclosed a primary bronchiogenic adenocarcinoma which streamed into the lung field, with widespread tumor metastasis assuming an extremely striking and characteristic alveolar pattern. Our error in diagnosis underscores the fact that considerable caution should be employed in labelling any condition primary alveolar tumor, unless very careful search has excluded a primary bronchial site; even if the latter is not discovered, it may simply have disappeared under advancing metastatic invasion.

We do not feel that primary alveolar carcinoma is necessarily a nonexistent condition, but do find reason to support a contention that it is not as common as has been reported. Analysis of our case would appear to add further weight to an impression that alveolar tumors are frequently metastatic in type, and need not represent true primary malignancy.

SUMMARY

1. After reviewing various opinions concerning persistence of alveolar epithelium in the human being, it is considered that existence of a residual cell membrane of this type has been established.

2. Survey of the literature also indicates, although opinion is by no means unanimous, that metaplastic and even neoplastic changes may develop in alveoli after exposure to various irritants or carcinogens. This may well occur in those with genetic predisposition to such.

3. We have reviewed similarities in pathology and dissimilarities in etiology between this reported condition in human beings and Jaagziekte in sheep.

4. Characteristics said to identify human primary alveolar cell carcinoma include multicentricity of pulmonary lesions, reduplication of alveolar pattern by cells whose morphology is dissimilar to that seen in other malignancies, and failure to identify a primary site elsewhere, including bronchial mucosa.

5. A case is described in detail. Diagnosis of primary alveolar carcinoma seemed well established through histopathologic examination of bronchoscopic biopsy material, resected pulmonary tissue, and gross autopsy findings, as well as through exfoliative studies of bronchoscopic aspirations and sputum.

6. It is of interest that we believed a diagnosis of alveolar carcinoma had been made before surgical intervention; if this had finally been confirmed, C. K. would have represented the second such patient described in the literature to date.

7. Microscopic autopsy section study, however, definitely disclosed true primary bronchiogenic adenocarcinoma. Clearly identified metastasis was extensive to lung and other viscera, and had definitely assumed that pattern described as typical of alveolar cell tumor.

8. Study of this case, in reference to others previously reported, would infer that several of the latter might not have represented true primary alveolar carcinoma. Some support is offered Herbut's contention that none are of the latter type, and that true bronchiogenic origin was not established simply because of disappearance under metastatic invasion.

9. Naturally, we suggest no final conclusion, but do believe that report of this case may contribute to further clarification of that question.

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THE LATERAL COSTAL BRANCH OF THE INTERNAL MAMMARY ARTERY

BENJAMIN N. KROPP, PH.D.
KINGSTON, ONTARIO

IN DISSECTING room subjects there is sometimes encountered a thoracic artery arising from the internal mammary near its origin and running laterally downward on the inner wall of the chest. The apparent frequency of its occurrence, its occasional large size, and the absence of its mention in many anatomic books of reference are striking, especially in view of the obvious importance of such a structure in paracentesis and other surgical procedures of the thorax.

The artery was known to the older anatomists. Henle (1876) describes an arteria mammaria interna lateralis which arises from the internal mammary near its entrance into the thorax and descends on the inner surface of four to six upper ribs and anastomoses with the corresponding intercostal arteries. He quotes Heister (1730) as having seen it in a 3-year-old child as well as in adult subjects. Henle pictures it with a good two-color illustration, and states that in thoracentesis or by traumatic damage the artery may be injured, and dangerous hemorrhage result. Otto (1830) calls it ramus costalis lateralis, a name retained by Rauber-Kopsch (1941) and others. Macalister (1889) reports having seen it of enormous size in a case of obliteration of the dorsal aorta from pressure of an intrathoracic tumor. In his extensive study of the arterial system of the Japanese, Adachi (1928) gives data on its frequency of occurrence, and notes also that it may arise as a branch of the subclavian or supreme intercostal arteries. Although it has not been investigated from the comparative anatomic viewpoint, it is interesting that Morestin (1894) reports it widely present in certain monkeys. Bean (1905) found the artery present five times in twenty-eight American mullatoes. However, when seen and remarked upon by anatomists, it has usually been considered an anomaly of rarer occurrence than the data would indicate. The artery is known under a variety of names, summarized in Table I.

The oldest term applied to the artery seems to be lateral internal mammary artery, given by Heister in 1730 and adopted by Henle. That name, however, seems to imply a constancy of occurrence which the artery does not possess. *Lateral costal branch* of the internal mammary artery is adequately descriptive and is used in this report.

In the present study 112 white subjects, all but eight of them males, were examined. The artery was seen in but one female. No precise data are avail-

From the Department of Anatomy, Queen's University Medical School.
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TABLE I.

NAME	AUTHOR
Lateral costal branch	Otto, 1830 v. Langer & Toldt, 1902 Cunningham, 1937 Rauber-Kopsch, 1941 Morris, 1942
Internal thoracic artery	Hodges, 1867
Lateral internal mammary artery	Henle, 1876 Morestin, 1894 Adachi, 1928
Retrocostal artery	Hellema, 1862 (cited from Henle)
Subcostal artery	Tiedemann (cited from Henle)
Lateral infracostal artery	Macalister, 1889 Toldt, 1926
Mammaire interne accessoire	Poirier et Charpy, 1902
Median intercostal artery	Hyrtl (cited from Poirier & Charpy)
Lateral thoracic artery	Bean, 1905

able as to age of this series, although almost all were over 60 years. In thirty-one individuals (27.6 per cent) the artery was present on one or both sides. When present on one side only it occurred more frequently on the left than on the right. The frequency of occurrence is summarized in Table II.

TABLE II.

Number of Subjects—112		
Artery present on right side only	10	8.9%
Artery present on left side only	15	13.4%
Artery present on both sides	6	5.3%
Total subjects in which artery present	31	27.6%

Adachi's data from 172 lateral chest walls are not significantly different from the above. When present bilaterally the lateral costal branch is not necessarily the same length on the two sides. The variation in length, as indicated by the frequency with which a given number of intercostal spaces were traversed, is shown in Table III.

TABLE III.

INTERCOSTAL SPACES TRAVERSED	1	2	3	4	5	6	TOTAL
Right side	2	3	4	5	1	1	16
Left side	3	6	4	5	1	2	21

When present, the lateral costal branch arises from the internal mammary artery at or immediately above the superior border of the first rib (Fig. 1). It passes downwards, backwards, and laterally from its origin, covered only by parietal pleura. In its course the artery approximates the midaxillary line, although it has been observed lying well forward toward the mammary line. Contrary to Adachi's observation, none of our specimens took origin from the subclavian or supreme intercostal arteries. Variations were seen, however, in its origin from the internal mammary; in one case it arose 1 cm.

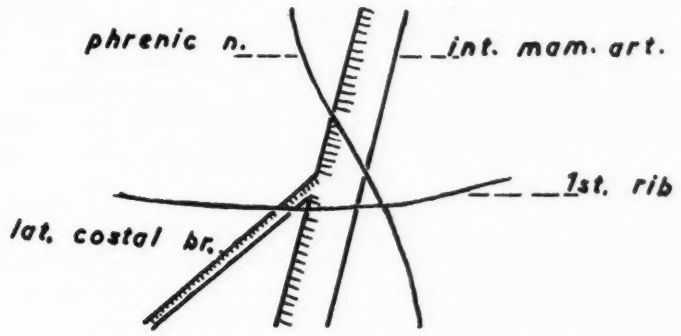

Fig. 1.—Right side. Diagram showing origin and direction of lateral costal branch of internal mammary artery, and usual relation to phrenic nerve and upper border of first rib.

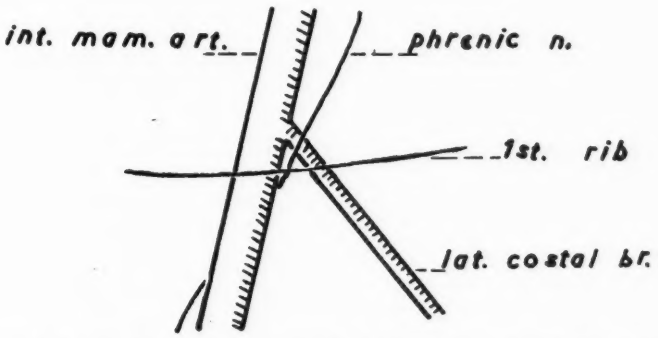

Fig. 2.—Left side. Diagram of occasional course of phrenic nerve over lateral costal branch.

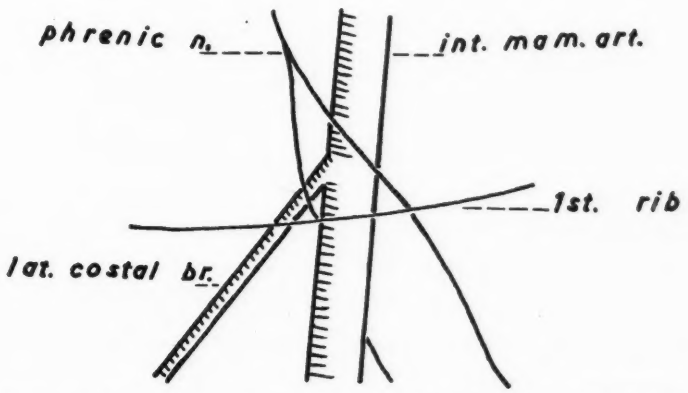

Fig. 3.—Right side. Diagram of usual course of branched phrenic nerve with relation to lateral costal branch and internal mammary artery.

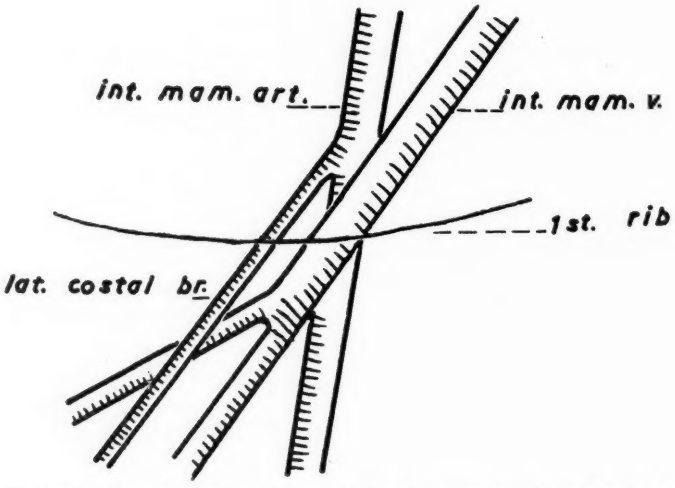

Fig. 4.—Right side. Diagram showing relation of internal mammary vein to lateral costal branch.

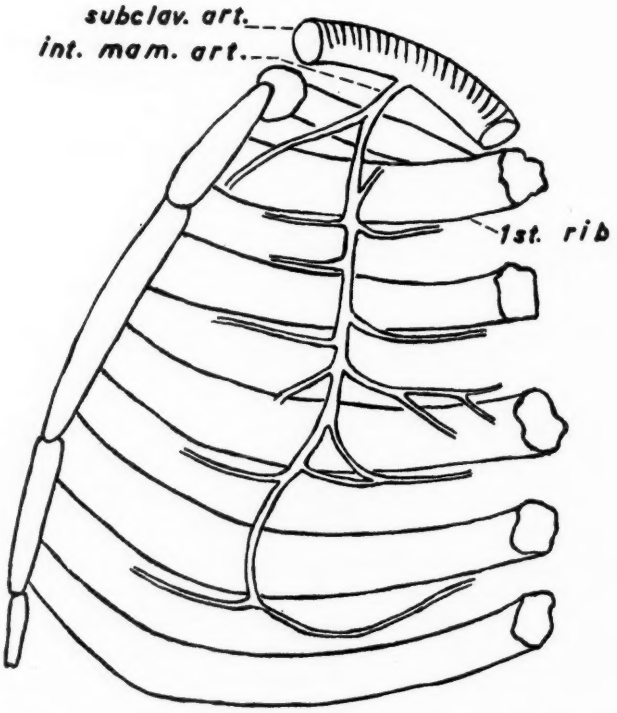

Fig. 5.—Right side. Hemisection, pleural surface. Diagram of typical distribution pattern of lateral costal branch.

above the upper border of the first rib and in another at the level of the lower border. On the right side the usual relation to the phrenic nerve is seen (Fig. 1), the nerve passing over the internal mammary and above the lateral costal branch. In two instances on the left side and once on the right, the nerve passed over the lateral costal branch and deep to the internal mammary artery behind the first rib (Fig. 2). Fig. 3 represents a case in which the divided nerve sent one small branch under the internal mammary after passing over the origin of the lateral costal, while the larger nerve maintained its usual relation to the internal mammary artery. No case was observed in which the phrenic nerve passed under both arteries or under the lateral costal and over the internal mammary.

The caliber of the artery varies with its length and the number of its anastomosing branches. When it extends over six or more intercostal spaces, it has been observed as large as the internal mammary. When viewed from within the thorax the lateral costal branch may be traced with ease beneath the pleura (Fig. 5), with branches given off in each intercostal space both anteriorly and posteriorly, usually at the lower border of the ribs. Branches may pass downwards over one or two ribs, however, before becoming continuous with the intercostal arteries. Occasional small twigs merely cross the pleural surface of a rib, or penetrate the rib as nutrient arteries. Near its termination the lateral costal branch usually describes a curve convex anteriorly. Bean (1905) states that the artery may reach the diaphragm, but no such extensive example was seen in the present series. The artery is accompanied by two veins between which it lies. The veins (Fig. 4) unite deep to the artery behind the first rib, then pass over the internal mammary artery to empty into the subclavian vein.

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ANESTHETIC EXPLOSIONS

Case Report

Maurice G. Buckles,* M.D., F.A.C.S., Columbus, Ohio

VERY little, if any, material on anesthetic explosions has been presented from the standpoint of the thoracic surgeon, and a very few cases of survivals in an anesthetic explosion have been reported, so that I feel it behooves one with this experience to record it, particularly with reference to management. It is quite probable that the pulmonary manifestations presented in this paper are primarily due to the blast of the explosion and simulate to a degree the blast noted in warfare, as well as in civilian life. There is little doubt that such changes in intrapulmonic pressure result in serious pulmonary conditions.

The author has no claims of being an anesthesiologist, and makes no pretense of discussing the various techniques of anesthesia, the chemistry of anesthetic agents, or the fine points of anesthesia as a whole. The following report is a case in which the author was called upon to aid in such an explosion, and was immediately available. An attempt is made to recite as accurately as possible the findings, the management, and the clinical course.

The occurrence of anesthetic explosions in the operating room is statistically uncommon. It is still too frequent, however, considering the danger to the patient, the operating room personnel, and the physical surroundings. Inasmuch as there has been no apparent decrease in the number of explosions, despite the numerous precautions recommended and undoubtedly practiced in connection with anesthesia,[1] it is important that the results and sequelae of such an explosion occurring to a patient under anesthesia be immediately recognized and handled expediently. This may tend to reduce the morbidity and mortality from such an accident.

The anesthetic explosion recently encountered resulted in severe hemorrhage into the paraorbital tissues; lacerations of the nasopharynx with profuse hemorrhage; prolonged hemorrhage from the tracheobronchial tree; production of a bilateral hemorrhagic pneumonia; spontaneous pneumothorax with an accompanying subcutaneous and mediastinal emphysema and pneumopericardia. The case report, which follows, presents the successful management; and also serves as a reminder that this dangerous accident still occurs.

CASE REPORT

H. S., a 56-year-old married white man, entered the hospital on Jan. 16, 1950, for the treatment of glaucoma. There was an associated diabetes mellitus, and hypertension—the blood pressure being 170/110.

On the fifth hospital day (Jan. 21, 1950) the patient was taken to surgery for an operation on the right eye. Anesthesia consisted of intravenous sodium pentothal with oxygen and nitrous oxide which was administered through a nasopharyngeal tube. Surgery consisted of cyclodiathermy to the right eye.

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At the conclusion of the operation there was a loud explosion, and the nasopharyngeal tube was blown out of the patient's nose, followed by profuse hemorrhage from the nose and mouth. His condition quickly became critical; the blood pressure dropped to 80/40; respirations were labored, and he became quite cyanotic. The author, who happened to be in the hospital, was called to see the patient. A 7 mm. bronchoscope was passed immediately with suction and aspiration of a large quantity of blood from the tracheobronchial tree. The patient resumed fairly normal respiration, and the cyanosis was relieved. The blood pressure gradually rose to 140/60. However, hemorrhage continued from the tracheobronchial tree, nasopharynx, and into the paraorbital tissues with marked swelling of the right cheek. An incision was made inside the mouth to decompress the swelling of the right cheek, and a pressure bandage was placed over the eyes. The nasopharynx was packed through the mouth to control the hemorrhage and also to prevent blood from running into the trachea; the anterior nares were then packed with gel foam. The bronchoscope was left in place for fifty minutes, but bleeding from the tracheobronchial tree continued, so an endotracheal tube was inserted to facilitate aspiration and to maintain an adequate airway. The patient was returned to his room in fair condition.

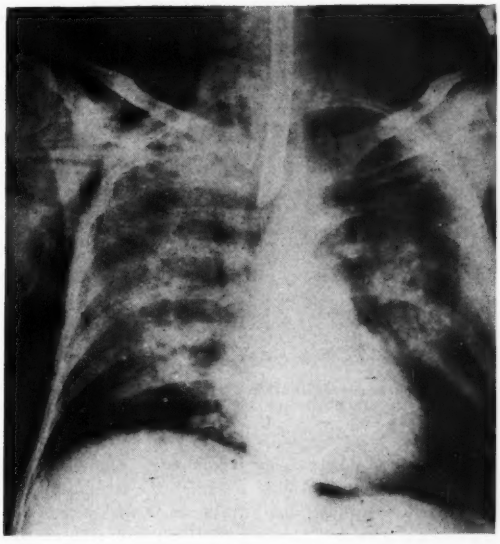

Fig. 1.—Portable chest roentgenogram following the explosion revealing subcutaneous emphysema, bilateral pulmonary infiltration, right pneumothorax, and mediastinal emphysema.

After returning to his room, the patient was placed on continuous oxygen, the tracheobronchial tree was aspirated frequently, and a blood transfusion was started. There were definite Cheyne-Stokes respirations for the first hour after being returned to his room, and he did not regain consciousness for about three hours. After receiving 500 c.c. of blood, the blood pressure was 100/70, the rectal temperature was 101.2° F., pulse 104, and respirations 26. Parenteral penicillin was started.

On the afternoon following the explosion, subcutaneous emphysema developed over the right anterior chest. Bleeding from the tracheobronchial tree continued, and about 600 c.c. of bloody fluid had been aspirated through the endotracheal tube. However, hemorrhage from the nasopharynx and into the paraorbital tissues was apparently controlled. A portable chest roentgenogram examination (Fig. 1) was made which revealed marked subcutaneous emphysema of the thoracic wall and cervical area; marked bilateral infiltration of the lung fields, although more extensive on the right side; and a small pneumothorax space on the right side with mediastinal emphysema.

The following morning (Jan. 22, 1950) the patient appeared in fairly good condition. The blood pressure was normal (preoperative level), the subcutaneous emphysema had not increased, there was no dyspnea, and bleeding from the tracheobronchial tree had apparently stopped. The packing from the nasopharynx and nose was removed; also the endotracheal tube. Following this, the patient was able to breathe freely, and was quite comfortable.

In the afternoon of the second postoperative day (Jan. 23, 1950) the patient developed progressive respiratory distress, the subcutaneous emphysema increased and extended to the head and neck, and the degree of pneumothorax was greater by physical examination. An intercostal catheter was introduced on the right side and attached to underwater drainage. There was an immediate escape of air with relief of the dyspnea, and the patient was again comfortable.

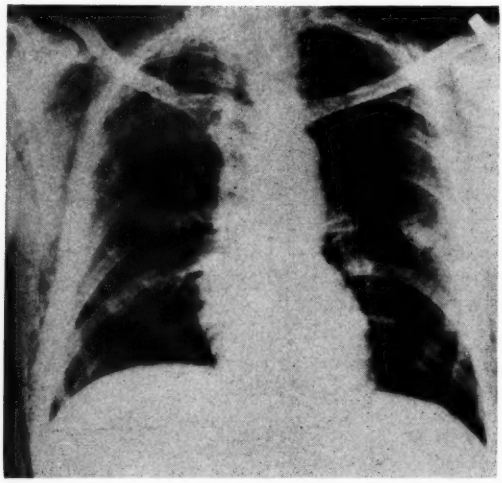

Fig. 2.—Chest roentgenogram examination on the fifth day showing clearing of the pulmonary infiltration, persistent subcutaneous and mediastinal emphysema, and evidence of pneumopericardia.

He rapidly improved, the subcutaneous emphysema diminished, breath sounds were good throughout both lung fields, and on Jan. 25, 1950, the intercostal catheter was removed. On Jan. 26, 1950, the temperature, pulse, and respirations were normal; a chest roentgenogram examination (Fig. 2) revealed marked clearing of the bilateral pulmonary infiltration, with persistence of the mediastinal and subcutaneous emphysema, and evidence of pneumopericardia.

In the evening of Jan. 26, 1950, the spontaneous pneumothorax recurred and was treated by repeated aspirations. By Jan. 28, 1950, the lung was reexpanded and his general condition was excellent. A chest roentgenogram examination on Feb. 2, 1950, revealed complete clearing of the lung fields and reexpansion of the right lung with some subcutaneous emphysema.

On the fourteenth day following the explosion, Feb. 4, 1950, the patient was discharged to the care of the ophthalmologist.

DISCUSSION

The exact mechanism of the anesthetic explosion in the case presented has not been ascertained; however, there are numerous reports concerning the explosions in the literature. The occurrence of such an accident should emphasize the importance of safety measures used to prevent such explosions, since prevention is the best method of treatment. Although it is stated that there has been no apparent reduction in the number of explosions despite the known

safety precautions, it is perhaps questionable how conscientiously all of the safety measures are practiced in all operating rooms by all of the operating room personnel. This is especially an important question since all too often the personnel are divided into those "who have" and those "who have not" witnessed an explosion with disastrous results. It is almost a certainty that those "who have" will never forget it.

It is obvious that the prevention of such explosions is of prime importance not only for the safety of the patient and personnel, but also from medicolegal viewpoints. A disastrous explosion in absence of or in violation of recommended safety precautions might produce a weak argument in court or in answering the questions of the patient's relatives.[3]

The recommended safety precautions have been summarized by Cole[2] as follows: the role of the manufacturer of anesthesia apparatus includes the production of equipment which will reduce the possibility of ignition of combustible gases. Precautions to be taken by the anesthetist include: (a) the avoidance of combustible agents in the presence of obvious hazards, such as the cautery; (b) eliminating the practice of washing out patient and apparatus with oxygen following an anesthesia; (c) use of caution in spilling gas; (d) employment of the intercoupler or the maintaining of continuous contact by the anesthetist with patient and machine; (e) use of the rebreathing technique; (f) washing tubes, bags, and mask with water or calcium chloride solution; (g) elimination of unnecessary, sudden movements by the anesthetist, and of unnecessary adjustments of the mask. The duties of the hospital are: (a) the installation of safe lights, switches, and electrical wiring; (b) the maintenance of a high humidity in the operating room; (c) prohibition of wool, silk, and ordinary rubber; (d) banning of visitors from the area surrounding the anesthetic apparatus; (e) banning of open flame, cigarettes, etc., from the operating room; and (f) the construction of grounded, conductive floors.

SUMMARY

1. A case report of an anesthetic explosion has been presented to demonstrate a method of handling such an accident, and also as a reminder of the constant danger involved in handling anesthetic gases.

2. The case involved was marked by severe hemorrhage into the paraorbital tissues; hemorrhage from lacerations of the nasopharynx; prolonged hemorrhage from the tracheobronchial tree; production of a bilateral hemorrhagic pneumonia; a spontaneous pneumothorax with subcutaneous and mediastinal emphysema, and pneumopericardia.

3. The importance of recognizing the potential explosive hazard of all inhalation anesthetics, and using accepted precautionary measures to prevent such accidents is emphasized.

4. The accepted safety measures are reviewed.

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THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

THIRTY-FIRST ANNUAL MEETING
APRIL 16, 17 AND 18, 1951, CHALFONTE-HADDON HALL
ATLANTIC CITY, N. J.

PROGRAM

Monday Morning, April 16, 1951

9:00 A.M. BUSINESS MEETING

9:30 A.M. SCIENTIFIC SESSION

1. **Progressive Changes of Pulmonary Function After Pneumonectomy: The Influence of Thoracoplasty, Pneumothorax, Oleothorax and Plastic Sponge Plombage on the Pneumonectomized Side**
   Edward A. Gaensler (by invitation) and John W. Strieder, Boston, Mass.
2. **Pulmonary Function in Traumatic Hemothorax Treated by Decortication**
   James H. Forsee and Major Stephan L. Kylar (by invitation), Denver, Colo.
3. **Late Changes in Ventilatory Function Following Thoracoplasty**
   S. R. Powers, Jr. (by invitation), and A. Himmelstein, New York, N. Y.
4. **Lung Function Studies in Poudrage Treatment of Recurrent Spontaneous Pneumothorax**
   Lt. Col. John Paul (by invitation), Edward J. Beattie, Jr., and Brian Blades, Washington, D. C.
5. **Effect of Position on the Rise in Carbon Dioxide Tension During Thoracic Surgery and the Effect of Artificial Ventilation in the Several Positions**
   Henry K. Beecher, Thomas J. Quinn, Jr., John P. Bunker, and Genesio L. D'Alessandro (all by invitation), Boston, Mass.
6. **Mucoid Impaction of the Bronchi**
   Robert R. Shaw, Dallas, Texas

Monday Afternoon, April 16, 1951

2:00 P.M. SCIENTIFIC SESSION

7. **Changes in Urine and Serum Electrolytes and Plasma Volume, After Major Intrathoracic Operations**
   Robert K. Finley, Jr. (by invitation), John Y. Templeton, III (by invitation), Robert H. Holland (by invitation) and John H. Gibbon, Philadelphia, Pa.
8. **The Treatment of Cardiospasm: Analysis of a Twelve-Year Experience**
   Arthur M. Olsen (by invitation), Stuart W. Farrington, Herman J. Moersch, and Howard A. Andersen (by invitation), Rochester, Minn.
9. **Considerations as to Etiology and Treatment of Achalasia of the Esophagus**
   Earle B. Kay, Cleveland, Ohio
10. **Complications and Surgical Treatment of Hiatus Hernia and Short Esophagus**
    Donald B. Effler, Cleveland, Ohio
11. **Formation of a Temporary External Esophageal Fistula Over a T-Tube for Stenosing Esophagitis**
    Philip Thorek (by invitation), Chicago, Ill.
12. **Endoscopic Sponge Biopsy**
    Max G. Carter (by invitation), Clinton A. Piper (by invitation), and Robert Nesbitt (by invitation), New Haven, Conn.

Tuesday Morning, April 17, 1951

9:00 A.M. SCIENTIFIC SESSION

13. **Thoracoplasty Combined With Resection for Pulmonary Tuberculosis**
William S. Conklin and Jerome T. Grismer (by invitation), Portland, Ore.

14. **Results in 278 Patients Who Had Modern Type of Thoracoplasty for Tuberculosis**
William M. Lees, Stephen C. H. Yang (by invitation), Michael Papoulakos (by invitation), Jan K. Bosch (by invitation), John Alexander, and Angel Larralde (by invitation), Ann Arbor, Mich.

15. **Simultaneous Decortication and Resection in Ineffective Pneumothorax**
Arnold O. Riley (by invitation) and Victor Kaunitz (by invitation), Mount Morris, N. Y.

16. **Decortication Preceding Thoracoplasty for Eradication of Long Standing (Up to Six Years) Chronic Tuberculous and Mixed Infection Empyema**
F. Douglas Ackman, Montreal, Canada

17. **Simple Excision in the Treatment of Pulmonary Tuberculosis**
Bernard J. Ryan (by invitation), Edgar M. Medlar (by invitation), Sunmount, N. Y., and Edward S. Welles, Saranac Lake, N. Y.

18. **Subscapular Paraffin Pack as a Supplement to Thoracoplasty as a Collapse Procedure**
W. E. Adams, William M. Lees, and James M. Fritz (by invitation), Chicago, Ill.

Tuesday Afternoon, April 17, 1951

2:00 P.M. EXECUTIVE SESSION

3:00 P.M. SCIENTIFIC SESSION

Address of the President—Alfred Blalock, Baltimore, Md.

19. **The Pathogenesis of Bronchopleural Fistulas Following Excisional Therapy for Pulmonary Tuberculosis**
G. N. Stemmermann (by invitation), C. Daniels (by invitation), and O. Auerbach, New York, N. Y.

20. **Bronchiectasis: A Comparative Study of Tuberculous and Nontuberculous Pyogenic Suppurative Disease**
Joseph Gordon, Ray Brook, N. Y., and Philip C. Pratt (by invitation), Saranac Lake, N. Y.

21. **The Prognosis of Residual Bronchiectasis After Incomplete Resection**
George P. Rosemond, W. Emory Burnett, and Joan-Humphrey Long (by invitation), Philadelphia, Pa.

7:00 P.M. COCKTAIL PARTY—CHALFONTE-HADDON HALL

8:00 P.M. BANQUET—CHALFONTE-HADDON HALL
DANCING

Wednesday Morning, April 18, 1951

9:00 A.M. SCIENTIFIC SESSION

22. **Radical Pneumonectomy**
William G. Cahan (by invitation), William L. Watson, and John L. Pool, New York, N. Y.

23. **A Preliminary Report of 26 Cases of Pulmonary Resection With Pleurectomy**
Bert H. Cotton and John R. F. Penido (by invitation), Beverly Hills, Calif.

24. **The Management of the Patient With Inoperable Cancer of the Chest**
Richard H. Meade, Jr. and Richard A. Rasmussen, Grand Rapids, Mich.

25. **Radio Active Isotopes in the Palliative Management of Carcinomatosis of the Pleura**
Edward M. Kent and Campbell Moses (by invitation), Pittsburgh, Pa.

26. **Identification of Regional Lymph Nodes in the Treatment of Bronchiogenic Carcinoma**
Joseph A. Weinberg, Long Beach, Calif.
27. **Pneumonectomy for Severe Irradiation Damage of Lung**
Martin Bergmann (by invitation) and Evarts A. Graham, St. Louis, Mo.

Wednesday Afternoon, April 18, 1951

2:00 P.M. SCIENTIFIC SESSION

28. **Reconstructive Surgery of the Trachea and Bronchi: Late Results With Dermal Grafts**
Paul W. Gebauer, Honolulu, Hawaii
29. **Myxochondroma of the Trachea: A Case Report**
Byron H. Evans, Los Angeles, Calif.
30. **Analysis of Twenty-Four Cases of Acute Cardiac Arrest**
J. L. Ehrenhaft, D. W. Eastwood (by invitation), and L. E. Morris (by invitation), Iowa City, Iowa.
31. **Constrictive Pericarditis and Constrictive Pleuritis Treated by Pericardectomy and Pulmonary Decortication**
Richard H. Overholt, C. Sidney Burwell (by invitation), John W. Woodbury (by invitation), and James H. Walker (by invitation), Boston, Mass.
32. **The Direct (Brock) Relief of Pulmonary Stenosis in Tetralogy of Fallot**
Robert P. Glover, Charles P. Bailey, and Thomas J. E. O'Neill (by invitation), Philadelphia, Pa.
33. **Treatment of Coronary Artery Insufficiency by Implantation of the Internal Mammary Artery into the Left Ventricular Myocardium**
Arthur Vineberg, Montreal, Canada

PAPERS TO BE READ BY TITLE

1. **Further Discussion of the Right Thoracic Approach to Esophageal Lesions**
R. K. Hollingsworth, Martinsburg, W. Va.
2. **Congenital Cystic Disease of Lung Associated With Anomalous Arteries**
Frederick G. Kergin, Toronto, Canada
3. **Transpleural Bronchotomy**
Alfred Goldman, Beverly Hills, Calif.